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(54) **ADAMANTANE ANALOGS**

(75) Inventors: **William F. DeGrado**, San Francisco, CA (US); **Jun Wang**, Philadelphia, PA (US)

(73) Assignee: **The Trustees Of The University of Pennsylvania**, Philadelphia, PA (US)

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C07D 209/56 (2006.01)

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C07D 233/61 (2006.01)

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CPC **A61K 31/44** (2013.01); **C07D 233/61** (2013.01); **C07D 339/08** (2013.01); **C07D 471/08** (2013.01)

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CPC . A61K 31/132; A61K 31/438; A61K 31/439;
C07D 209/56; C07D 209/96

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546/17, 18, 72

See application file for complete search history.

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Primary Examiner — Kamal Saeed

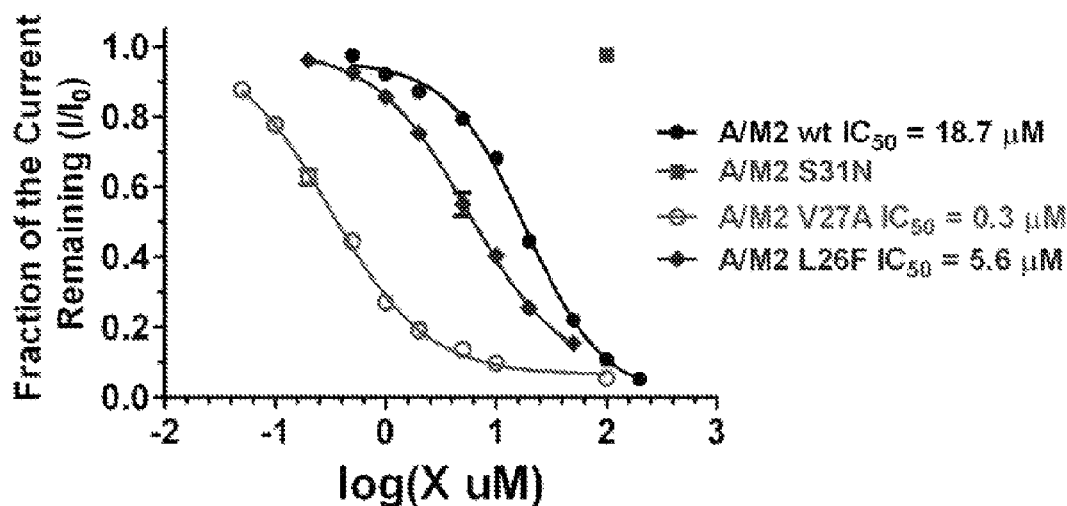
Assistant Examiner — Janet L Coppins

(74) *Attorney, Agent, or Firm* — Baker & Hostetler LLP

(57) **ABSTRACT**

Provided are compounds that are capable of modulating the activity of the influenza A virus via interaction with the M2 transmembrane protein. Also provided are methods for treating an influenza A-affected disease state or infection comprising administering a composition comprising one or more compounds that have been identified as being capable of interaction with the M2 protein.

14 Claims, 1 Drawing Sheet



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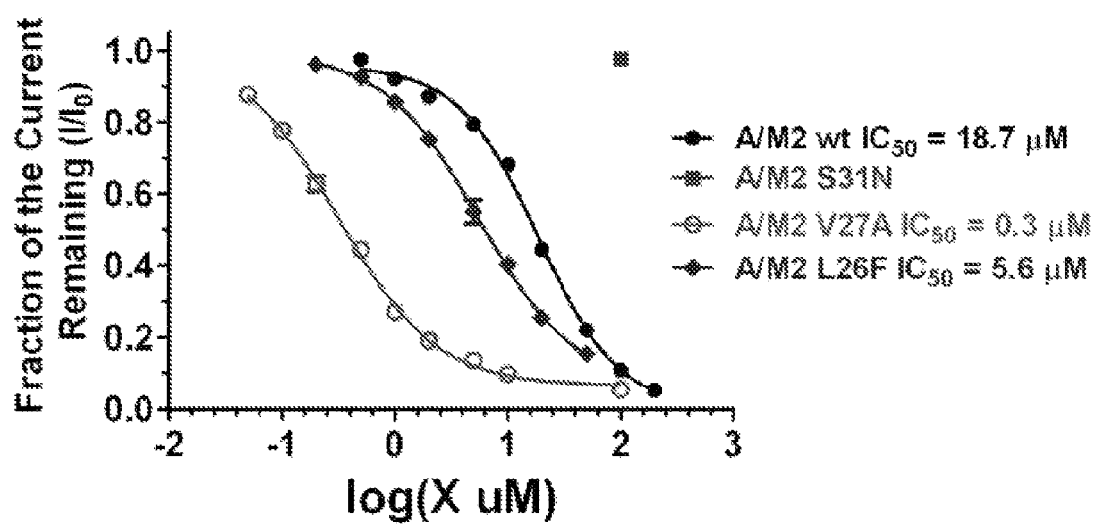
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ADAMANTANE ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is the National Stage of International Application No. PCT/US2010/043974, filed Jul. 30, 2010, which claims the benefit of U.S. Provisional Application No. 61/235,870, filed Aug. 21, 2009, the disclosures of which are incorporated herein by reference in their entireties.

STATEMENT OF GOVERNMENT RIGHTS

Research leading to the disclosed invention was funded in part by the U.S. National Institutes of Health, grant number U01 74571 (William F. DeGrado). Accordingly, the United States Government has certain rights in the invention described herein.

TECHNICAL FIELD

The present invention pertains to, among other things, compounds and methods for modulating the activity of the influenza virus.

BACKGROUND

The M2 protein is found in the viral envelope of influenza A virus and functions as a highly selective, pH-regulated proton channel important for the life cycle of the virus. Unlike neuraminidase inhibitors, rimantadine and amantadine are anti-viral agents capable of blocking the tetrameric M2 channel. In 2006, the CDC issued an alert instructing clinicians to avoid using M2 ion-channel inhibitors during influenza season due to the extraordinarily high frequency of amantadine resistance in influenza A isolates associated with a single point mutation in the M2 protein, S31N (Hayden F. G., *Antiviral Resistance in Influenza Viruses—Implications for Management and Pandemic Response*, *N Engl J Med*, 2006, 354; 8). The drug-binding site is lined by residues that are mutated in amantadine-resistant viruses. Grambas, S., Bennett, M. S. & Hay, A. J. *Influence of amantadine resistance mutations on the pH regulatory function of the M2 protein of influenza A viruses*. *Virology* 191, 541-549 (1992); Bright, R. A., Shay, D. K., Shu, B., Cox, N. J. & Klimov, A. I. *Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States*. *J. Am. Med. Assoc.* 295, 891-894 (2006). Recently, it has been reported that resistance to rimantadine and amantadine in humans, birds and pigs has reached more than 90%, casting into doubt the continued ability of these drugs alone to satisfy the need for treatment of influenza (Deyde, V. M. et al. *Surveillance of resistance to adamantanes among influenza A(H3N2) and A(H1N1) viruses isolated worldwide*. *J. Infect. Dis.* 196, 249-257 (2007)).

Previous studies have suggested that BL-1743 (3-(4,5-Dihydro-1H-imidazol-2-yl)-3-aza-spiro[5.5]undecane) interacts differently with the M2 proton channel as compared with amantadine, but have found that the majority of isolated influenza viruses that are amantadine-resistant are also resistant to BL-1743. Tu Q, et al., *Characterization of inhibition of M2 ion channel activity by BL-1743, an inhibitor of influenza A virus*, *J. Virol.* 1996 July; 70(7):4246-52. For example, Tu Q, et al. found that mutations known to confer amantadine resistance at M2 residues 27, 30, 31, and 34, all within the M2 transmembrane domain, also induce “complete” resistance to BL-1743. Id. The publication by Tu Q, et al. concluded that

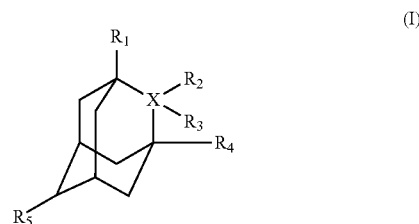
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“the overlapping spectra of amantadine and BL-1743 resistance mutations and the higher apparent K_i . . . do not indicate that BL-1743 should replace the use of amantadine (or rimantadine) for the prophylaxis or treatment of influenza virus infections in humans.” Id. See also Kurtz, et al., *Growth impairment resulting from expression of influenza virus M2 protein in Saccharomyces cerevisiae: identification of a novel inhibitor of influenza virus*. *Antimicrob Agents Chemother.* 1995 October; 39(10):2204-9 (“BL-1743 does not produce an additive effect on M2 inhibition, suggesting that these two compounds interact with similar sites in the M2 protein Thus, BL-1743 appears to represent a novel structure with an antiviral profile similar to that of amantadine.”).

Certain analogs of adamantane, such as amantadine and rimantadine, has been used for decades as inhibitors of the influenza A virus M2 protein (AM2) in the prophylaxis and treatment of influenza A infections, but its clinical use has been limited by its central nervous system (CNS) side effects as well as emerging drug-resistant strains of the virus. Although a large number of adamantane analogs have been reported in the literature, the detailed mechanism of inhibition has not been addressed, moreover, most of the compounds had not been tested against adamantane resistant mutants. Therefore, prior to the present invention, the question was unresolved as to whether the adamantane scaffold represents a worthwhile basis for drug discovery of M2 inhibitors.

SUMMARY

In one aspect of the present invention, provided are compounds having the formula (I):



wherein

X is carbon, nitrogen, alkylene, or alkyleneamino;

R₁ is hydrogen, deuterium, halo, hydroxyl, nitro, guanidiny, —(R₆)—guanidine, formamidinyl, carbonyl, oxime, amino, aminocarbonyl, aminooxy, aralkoxy, or aralkylaminoxy;

R₂ and R₃ are each independently hydrogen, deuterium, hydroxyl, carbonyl, amino, nitro, alkyl, trifluoromethyl, aryl, aminocarbonyl, or —C(=Y)—Z,

or

R₂ and R₃ taken together along with the atom to which they are both attached form a three- to six-membered carbocyclic or heterocyclic ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl;

Y is O, S, or NH;

Z is amino, —NH—NH₂, methoxy, or methylthio;

R₄ is hydrogen, deuterium, or amino;

R₅ is hydrogen or carbonyl; and,

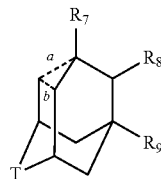
R₆ is alkylene or —NH—C(=NH)—;

or a stereoisomer, partial stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof,

3

with the proviso that if R_1 is amino, R_2 , R_3 , R_4 , and R_5 cannot all be hydrogen.

In another aspect, provided are compounds having the formula (II):



wherein

dashed lines a and b independently represent optional bonds, wherein at least one of a and b must be present as a bond;

T is alkylene;

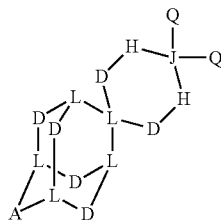
R_7 is hydrogen, deuterium, halo, hydroxyl, nitro, guanidinyl, -(alkylene)-guanidine, formamidinyl, carbonyl, oxime, amino, aminocarbonyl, aminooxy, aralkoxy, or aralkylaminoxy;

R_8 is hydrogen, deuterium, hydroxyl, carbonyl, amino, nitro, alkyl, trifluoromethyl, aryl, aminocarbonyl, or $\text{—NH—SO}_2\text{—NH}_2$; and,

R_9 is hydrogen, alkyl, hydroxyl, amino, nitro, aryl, guanidinyl, or -(alkylene)-guanidine;

or a stereoisomer, partial stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof.

In yet another aspect, provided are compounds having the formula (III):



wherein

A and each D are independently $\text{—(CH}_2\text{)}_n\text{—}$, $\text{—S(O)}_m\text{—}$, $\text{(CH}_2\text{)}_n\text{—}$, $\text{—(CH}_2\text{)}_n\text{—S(O)}_m\text{—}$, $\text{—O—(CH}_2\text{)}_n\text{—}$, $\text{—(CH}_2\text{)}_n\text{—O—}$, $\text{—NH—(CH}_2\text{)}_n\text{—}$, $\text{—(CH}_2\text{)}_n\text{—NH—}$, or $\text{—NCH}_3\text{—(CH}_2\text{)}_n\text{—}$, wherein one or both hydrogens in a CH_2 group may independently be substituted with halogen or $\text{C}_1\text{—C}_6$ alkyl, and wherein m and n are each independently 0-2, or,

A is a disubstituted quaternary carbon having substituents that are independently $\text{C}_1\text{—C}_6$ alkyl optionally substituted with halogen, or that, along with A, together form a 3- to 7-member carbocyclic or heterocyclic ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl;

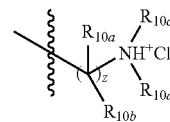
each H is independently $\text{—(CH}_2\text{)}_z\text{—}$, optionally substituted with halogen or $\text{C}_1\text{—C}_6$ alkyl;

z is 0-3;

J is carbon or nitrogen;

each Q is independently hydrogen, alkyl, amino, hydroxyl, carbonyl, nitro, amidinyl, guanidinyl, $\text{—(CH}_2\text{)}_z\text{—NH}_3^+\text{Cl}^-$, or

4



wherein each R_{10} is independently hydrogen or alkyl optionally substituted with halogen;

or,

both Q substituents together along with J form a 3- to 7-member carbocyclic or heterocyclic ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl;

each L is independently carbon, nitrogen, or silicon, except that no more than two L substituents are chosen as nitrogen, and no more than two L substituents are chosen as silicon;

or a stereoisomer, partial stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof.

In other aspects, provided are methods treating an influenza A virus-affected disease state or infection comprising the step of administering to a subject in need thereof a composition comprising a compound of formula (I), a compound of formula (II), a compound of formula (III), or any combination thereof.

Also provided are compositions for use in the treatment of an influenza A virus-affected disease state or infection comprising

a compound of formula (I), a compound of formula (II), a compound of formula (III), or any combination thereof and, a pharmaceutically acceptable carrier, diluent, or excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts dose response curves for an exemplary compound according to the present invention on the inhibition of wild-type influenza virus, as well as on the V27A, L26F, and S31N mutants.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures and examples, which form a part of this disclosure. It is to be understood that this invention is not limited to the specific products, methods, conditions or parameters described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention.

The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, in their entirety.

As employed above and throughout the disclosure, the following terms and abbreviations, unless otherwise indicated, shall be understood to have the following meanings

In the present disclosure the singular forms “a,” “an,” and “the” include the plural reference, and reference to a particular numerical value includes at least that particular value, unless the context clearly indicates otherwise. Thus, for example, a reference to “a compound” is a reference to one or more of such compounds and equivalents thereof known to those skilled in the art, and so forth. Furthermore, when

indicating that a certain chemical moiety “may be” X, Y, or Z, it is not intended by such usage to exclude other choices for the moiety; for example, a statement to the effect that R₁ “may be alkyl, aryl, or amino” does not exclude other choices for R₁, such as halo, aralkyl, and the like.

When values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another embodiment. As used herein, “about X” (where X is a numerical value) preferably refers to $\pm 10\%$ of the recited value, inclusive. For example, the phrase “about 8” refers to a value of 7.2 to 8.8, inclusive; as another example, the phrase “about 8%” refers to a value of 7.2% to 8.8%, inclusive. Where present, all ranges are inclusive and combinable. For example, when a range of “1 to 5” is recited, the recited range should be construed as including ranges “1 to 4,” “1 to 3,” “1-2,” “1-2 & 4-5,” “1-3 & 5,” and the like. In addition, when a list of alternatives is positively provided, such listing can be interpreted to mean that any of the alternatives may be excluded, e.g., by a negative limitation in the claims. For example, when a range of “1 to 5” is recited, the recited range may be construed as including situations whereby any of 1, 2, 3, 4, or 5 are negatively excluded; thus, a recitation of “1 to 5” may be construed as “1 and 3-5, but not 2,” or simply “wherein 2 is not included.” In another example, when a listing of possible substituents including “hydrogen, alkyl, and aryl” is provided, the recited listing may be construed as including situations whereby any of “hydrogen, alkyl, and aryl” is negatively excluded; thus, a recitation of “hydrogen, alkyl, and aryl” may be construed as “hydrogen and aryl, but not alkyl,” or simply “wherein the substituent is not alkyl”.

As used herein, the terms “component,” “composition of compounds,” “compound,” “drug,” “pharmacologically active agent,” “active agent,” “therapeutic,” “therapy,” “treatment,” or “medicament” are used interchangeably herein to refer to a compound or compounds or composition of matter which, when administered to a subject (human or animal) induces a desired pharmacological and/or physiologic effect by local and/or systemic action.

The abbreviations in the specification correspond to units of measure, techniques, properties, or compounds as follows: “min” means minute(s), “g” means gram(s), “mg” means milligram(s), “ μ g” means microgram(s), “eq” means equivalent(s), “h” means hour(s), “ μ L” means microliter(s), “mL” means milliliter(s), “mM” means millimolar, “M” means molar, “mmol” or “mmole” means millimole(s), “cm” means centimeters, “SEM” means standard error of the mean, and “IU” means International Units. “IC₅₀ value” or “IC₅₀” means dose of the compound which results in 50% alleviation or inhibition of the observed condition or effect.

As used herein, “alkyl” refers to an optionally substituted, saturated straight, or branched, hydrocarbon radical having from about 1 to about 20 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein). Where appropriate, “alkyl” can mean “alkylene”; for example, if X is —R₁R₂, and R₁ is said to be “alkyl”, then “alkyl” may correctly be interpreted to mean “alkylene”.

“Amino” refers to —NH₂ and may include one or more substituents that replace hydrogen. “Amino” is used interchangeably with amine and is also intended to include any pharmaceutically acceptable amine salts. For example, amino may refer to —NH⁺(X)(Y)Cl[−], wherein X and Y are preferably and independently hydrogen or alkyl, wherein alkyl may include one or more halo substitutions.

As used herein, “aryl”, “arene”, and “aromatic” each refer to an optionally substituted, saturated or unsaturated, mono-

cyclic, polycyclic, or other homo- or heterocyclic aromatic ring system having from about 3 to about 50 ring members (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 5 to about 10 ring atom members being preferred. Such moieties encompass (include) “heteroaryl” and “heteroarene” as defined infra. Where appropriate, “aryl” can mean “arene”; for example, if X is —R₁R₂, and R₁ is said to be “aryl”, then “aryl” may correctly be interpreted to mean “arene”.

As used herein, “alkenyl” refers to an alkyl radical having from about 2 to about 20 carbon atoms and one or more double bonds (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), wherein alkyl is as previously defined. In some embodiments, it is preferred that the alkenyl groups have from about 2 to about 6 carbon atoms. Alkenyl groups may be optionally substituted.

As used herein, “aralkyl” refers to alkyl radicals bearing one or more aryl substituents and having from about 4 to about 50 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), wherein aryl and alkyl are as previously defined. In some preferred embodiments, the alkyl moieties of the aralkyl groups have from about 1 to about 4 carbon atoms. In other preferred embodiments, the alkyl moieties have from about 1 to about 3 carbon atoms. Aralkyl groups may be optionally substituted.

“Alkylamino” signifies alkyl-(NH)—, wherein alkyl is as previously described and NH is defined in accordance with the provided definition of amino. “Arylamino” represents aryl-(NH)—, wherein aryl is as defined herein and NH is defined in accordance with the provided definition of amino. Likewise, “aralkylamino” is used to denote aralkyl-(NH)—, wherein aralkyl is as previously defined and NH is defined in accordance with the provided definition of amino. “Alkylamido” refers to alkyl-CH(=O)NH—, wherein alkyl is as previously described. “Alkoxy” as used herein refers to the group R—O— where R is an alkyl group, and alkyl is as previously described. “Aralkoxy” stands for R—O—, wherein R is an aralkyl group as previously defined. “Alkylsulfonyl” means alkyl-SO₂—, wherein alkyl is as previously defined. “Aminoxy” as used herein refers to the group amino-(O)—, wherein amino is defined as above. “Aralkylaminoxy” as used herein is used to denote aryl-alkyl-aminoxy-, wherein aryl, alkyl, and aminoxy are respectively defined as provided previously.

As used herein, “alkylene” refers to an optionally branched or substituted bivalent alkyl radical having the general formula —(CH₂)_n—, where n is 1 to 10. Non-limiting examples include methylene, trimethylene, pentamethylene, and hexamethylene.

“Alkyleneamino” refers to —(CH₂)_n—NH—, where n is 1 to 10 and wherein the bivalent alkyl radical may be optionally branched or substituted, and the amino group may include one or more substituents that replace hydrogen.

As used herein, “heteroaryl” or “heteroarene” refers to an aryl radical wherein in at least one of the rings, one or more of the carbon atom ring members is independently replaced by a heteroatom group selected from the group consisting of S, O, N, and NH, wherein aryl is as previously defined. Heteroaryl/heteroarene groups having a total of from about 3 to about 14 carbon atom ring members and heteroatom ring members are preferred. Likewise, a “heterocyclic ring” is an aryl radical wherein one or more of the carbon atom ring members may be (but are not necessarily) independently replaced by a heteroatom group selected from the group consisting of S, O, N, and NH. Heterocyclic rings having a total from about 3 to 14 ring

members and heteroatom ring members are preferred, but not necessarily present; for example, "heterocyclohexyl" may be a six-membered aryl radical with or without a heteroatom group.

"Halo" and "halogen" each refers to a fluoro, chloro, bromo, or iodo moiety, with fluoro, chloro, or bromo being preferred.

"Haloalkyl" signifies halo-alkyl- wherein alkyl and halo, respectively, are as previously described.

The phrase reading "[moiety] is absent" means that the substituents to which the moiety is attached may be directly attached to each other.

Typically, substituted chemical moieties include one or more substituents that replace hydrogen. Exemplary substituents include, for example, halo (e.g., F, Cl, Br, I), alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, alkenyl, alkenyl, aralkyl, aryl, heteroaryl, heteroaralkyl, spiroalkyl, heterocycloalkyl, hydroxyl ($-\text{OH}$), nitro ($-\text{NO}_2$), cyano ($-\text{CN}$), amino ($-\text{NH}_2$), $-\text{N}$ -substituted amino ($-\text{NHR}$), $-\text{N,N}$ -disubstituted amino ($-\text{N(R)R}$), oxo ($=\text{O}$), carboxy ($-\text{COOH}$), $-\text{O}-\text{C}(=\text{O})\text{R}$, $-\text{C}(=\text{O})\text{R}$, $-\text{OR}$, $-\text{C}(=\text{O})\text{OR}$, $-(\text{alkylene})-\text{C}(=\text{O})-\text{OR}$, $-\text{NHC}(=\text{O})\text{R}$, aminocarbonyl ($-\text{C}(=\text{O})\text{NH}_2$), $-\text{N}$ -substituted aminocarbonyl ($-\text{C}(=\text{O})\text{NHR}$), $-\text{N,N}$ -disubstituted aminocarbonyl ($-\text{C}(=\text{O})\text{N(R)R}$), thiol, thiolato ($-\text{SR}$), sulfonic acid ($-\text{SO}_3\text{H}$), phosphonic acid ($-\text{PO}_3\text{H}$), $-\text{P}(=\text{O})(\text{OR})\text{OR}$, $-\text{S}(=\text{O})\text{R}$, $-\text{S}(=\text{O})_2\text{R}$, $-\text{S}(=\text{O})_2\text{NH}_2$, $-\text{S}(=\text{O})_2\text{NHR}$, $-\text{S}(=\text{O})_2\text{NR}$, $-\text{NHS}(=\text{O})_2\text{R}$, $-\text{NR}^+\text{S}(=\text{O})_2\text{R}$, $-\text{CF}_3$, $-\text{CF}_2\text{CF}_3$, $-\text{NHC}(=\text{O})\text{NHR}$, $-\text{NHC}(=\text{O})\text{NR}$, $-\text{NR}^+\text{C}(=\text{O})\text{NHR}$, $-\text{NR}^+\text{C}(=\text{O})\text{NR}$, $-\text{NR}^+\text{C}(=\text{O})\text{R}$ and the like. In relation to the aforementioned substituents, each moiety R can be, independently, any of H, alkyl, cycloalkyl, alkenyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl, for example.

As used herein, the terms "treatment" or "therapy" (as well as different word forms thereof) includes preventative (e.g., prophylactic), curative or palliative treatment.

As employed above and throughout the disclosure the term "effective amount" refers to an amount effective, at dosages, and for periods of time necessary, to achieve the desired result with respect to the treatment of the relevant disorder, condition, or side effect. It will be appreciated that the effective amount of components of the present invention will vary from patient to patient not only with the particular compound, component or composition selected, the route of administration, and the ability of the components to elicit a desired response in the individual, but also with factors such as the disease state or severity of the condition to be alleviated, hormone levels, age, sex, weight of the individual, the state of being of the patient, and the severity of the pathological condition being treated, concurrent medication or special diets then being followed by the particular patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. Dosage regimens may be adjusted to provide the improved therapeutic response. An effective amount is also one in which any toxic or detrimental effects of the components are outweighed by the therapeutically beneficial effects. As an example, the compounds useful in the methods of the present invention are administered at a dosage and for a time such that the level of activation and adhesion activity of platelets is reduced as compared to the level of activity before the start of treatment.

"Pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without

excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio.

Within the present invention, the disclosed compounds may be prepared in the form of pharmaceutically acceptable salts. "Pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. These physiologically acceptable salts are prepared by methods known in the art, e.g., by dissolving the free amine bases with an excess of the acid in aqueous alcohol, or neutralizing a free carboxylic acid with an alkali metal base such as a hydroxide, or with an amine.

Compounds described herein throughout, can be used or prepared in alternate forms. For example, many amino-containing compounds can be used or prepared as an acid addition salt. Often such salts improve isolation and handling properties of the compound. For example, depending on the reagents, reaction conditions and the like, compounds as described herein can be used or prepared, for example, as their hydrochloride or tosylate salts. Isomorphous crystalline forms, all chiral and racemic forms, N-oxide, hydrates, solvates, and acid salt hydrates, are also contemplated to be within the scope of the present invention.

Certain acidic or basic compounds of the present invention may exist as zwitterions. All forms of the compounds, including free acid, free base and zwitterions, are contemplated to be within the scope of the present invention. It is well known in the art that compounds containing both amino and carboxy groups often exist in equilibrium with their zwitterionic forms. Thus, any of the compounds described herein throughout that contain, for example, both amino and carboxy groups, also include reference to their corresponding zwitterions.

"Hydrate" refers to a compound of the present invention which is associated with water in the molecular form, i.e., in which the $\text{H}-\text{OH}$ bond is not split, and may be represented, for example, by the formula $\text{R} \cdot \text{H}_2\text{O}$, where R is a compound of the invention. A given compound may form more than one hydrate including, for example, monohydrates ($\text{R} \cdot \text{H}_2\text{O}$) or polyhydrates ($\text{R} \cdot n\text{H}_2\text{O}$ wherein n is an integer >1) including, for example, dihydrates ($\text{R} \cdot 2\text{H}_2\text{O}$), trihydrates ($\text{R} \cdot 3\text{H}_2\text{O}$), and the like, or hemihydrates, such as, for example, $\text{R} \cdot n/2\text{H}_2\text{O}$, $\text{R} \cdot n/3\text{H}_2\text{O}$, $\text{R} \cdot n/4\text{H}_2\text{O}$ and the like wherein n is an integer.

"Solvate" refers to a compound of the present invention which is associated with solvent in the molecular form, i.e., in which the solvent is coordinatively bound, and may be represented, for example, by the formula $\text{R} \cdot (\text{solvent})$, where R is a compound of the invention. A given compound may form more than one solvate including, for example, monosolvates ($\text{R} \cdot (\text{solvent})$) or polysolvates ($\text{R} \cdot n(\text{solvent})$) wherein n is an integer >1 including, for example, disolvates ($\text{R} \cdot 2(\text{solvent})$),

9

trisolvates ($R.3(\text{solvent})$), and the like, or hemisolvates, such as, for example, $R.n_2(\text{solvent})$, $R.n_3(\text{solvent})$, $R.n_4(\text{solvent})$ and the like wherein n is an integer. Solvents herein include mixed solvents, for example, methanol/water, and as such, the solvates may incorporate one or more solvents within the solvate.

"Acid hydrate" refers to a complex that may be formed through association of a compound having one or more base moieties with at least one compound having one or more acid moieties or through association of a compound having one or more acid moieties with at least one compound having one or more base moieties, said complex being further associated with water molecules so as to form a hydrate, wherein said hydrate is as previously defined and R represents the complex herein described above.

The term "stereoisomers" refers to compounds that have identical chemical constitution, but differ as regards the arrangement of the atoms or groups in space.

"Racemic" means having the capacity for resolution into forms of opposed optical activity.

As used herein, the term "partial stereoisomer" refers to stereoisomers having two or more chiral centers wherein at least one of the chiral centers has defined stereochemistry (i.e., R or S) and at least one has undefined stereochemistry (i.e., R or S). When the term "partial stereoisomers thereof" is used herein, it refers to any compound within the described genus whose configuration at chiral centers with defined stereochemistry centers is maintained and the configuration of each undefined chiral center is independently selected from R or S . For example, if a stereoisomer has three chiral centers and the stereochemical configuration of the first center is defined as having " S " stereochemistry, the term "or partial stereoisomer thereof" refers to stereoisomers having SRR , SRS , SSR , or SSS configurations at the three chiral centers, and mixtures thereof.

"Prodrug" refers to compounds which are themselves inactive or minimally active for the activity desired, but through biotransformation can be converted into biologically active metabolites. For example, a prodrug of the present invention would include, inter alia, any compound which is convertible in vivo by metabolic means to a compound claimed or described in the present disclosure.

"N-oxide" refers to compounds wherein the basic nitrogen atom of either a heteroaromatic ring or tertiary amine is oxidized to give a quaternary nitrogen bearing a positive formal charge and an attached oxygen atom bearing a negative formal charge.

When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

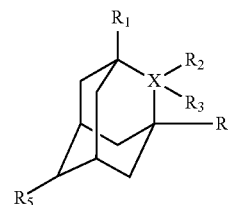
The term "administering" means either directly administering a compound or composition of the present invention, or administering a prodrug, derivative or analog which will form an equivalent amount of the active compound or substance within the body.

"Dosage unit" refers to physically discrete units suited as unitary dosages for the particular individual to be treated. Each unit may contain a predetermined quantity of active compound(s) calculated to produce the desired therapeutic effect(s) in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention may be dictated by (a) the unique characteristics of the active compound(s) and the particular therapeutic effect(s) to be achieved, and (b) the limitations inherent in the art of compounding such active compound(s).

10

"Subject" or "patient" refers to an embryonic, immature, or adult animal, including the human species, that is treatable with the compositions, and/or methods of the present invention.

Accordingly, in one aspect there are provided compounds having the formula (I):



(I)

wherein

X is carbon, nitrogen, alkylene, or alkyleneamino;

R_1 is hydrogen, deuterium, halo, hydroxyl, nitro, guanidinyl, $-(R_6)$ -guanidine, formamidinyl, carbonyl, oxime, amino, aminocarbonyl, aminooxy, aralkoxy, or aralkylaminooxy;

R_2 and R_3 are each independently hydrogen, deuterium, hydroxyl, carbonyl, amino, nitro, alkyl, trifluoromethyl, aryl, aminocarbonyl, or $-C(=Y)-Z$,

or

R_2 and R_3 taken together along with the atom to which they are both attached form a three- to six-membered carbocyclic or heterocyclic ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl;

Y is O , S , or NH ;

Z is amino, $-NH-NH_2$, methyloxy, or methylthio;

R_4 is hydrogen, deuterium, or amino;

R_5 is hydrogen or carbonyl; and,

R_6 is alkylene or $-NH-C(=NH)-$;

or a stereoisomer, partial stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof,

with the proviso that if R_1 is amino and X is methylene or ethylene, R_2 , R_3 , R_4 , and R_5 cannot all be hydrogen.

With respect to the compounds according to formula (I), certain provisos may apply. These provisos may also optionally apply pursuant to the presently disclosed methods. For example, if R_1 , R_4 , and R_5 are all hydrogen, and X is methylene, then if either of R_2 and R_3 are hydrogen, the other of R_2 and R_3 cannot be carbonyl. In addition, if R_2 , R_3 , R_4 , and R_5 are all hydrogen and X is methylene or ethylene, then R_1 cannot be amino. Furthermore, if R_2 , R_3 , R_4 , and R_5 are all hydrogen and X is methylene, then R_1 cannot be $-CH(NH^3+Cl^-)CH_2CH_3$. In addition, if R_1 , R_4 , and R_5 are all hydrogen, and X is methylene, then if either of R_2 and R_3 are hydrogen, the other of R_2 and R_3 cannot be amino.

In some embodiments, X may be carbon. With respect to such embodiments, R_2 , R_3 , R_4 , and R_5 may each be hydrogen. In such instances, R_1 may be guanidinyl, $-(R_6)$ -guanidine, formamidinyl, carbonyl, oxime, nitro, aminocarbonyl, aminooxy, aralkoxy, or aralkylaminooxy. In some embodiments of this type, R_6 may be $-CH(CH_2)-$ or $-NH-C(=NH)-$. Where R_2 , R_3 , R_4 , and R_5 are each hydrogen, R_1 may also be (5-methyl-3H-imidazol-4-ylmethylene)-aminooxy or hydroxyamino(imino)methyl.

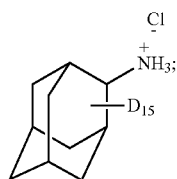
In other instances, R_1 and R_5 may both be hydrogen. With respect to such embodiments, R_2 may be hydrogen and R_3 may be hydrogen, hydroxyl, carbonyl, amino, nitro, or

11

—C(=Y)—Z. In other compounds wherein R_1 , R_2 , and R_5 are hydrogen, X may be nitrogen and R_3 may be hydrogen, hydroxyl, amino, or —C(=Y)—Z. In other instances where R_1 and R_5 are hydrogen, R_2 and R_3 may be taken together along with the atom to which they are both attached to form a three- to six-membered carbocyclic or heterocyclic ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl. For example, R_2 and R_3 may be taken together to form a six-membered heterocyclic ring substituted with amino, such as in the case of [1,3]Dithian-5-ylamine. In another example, R_2 and R_3 may be taken together to form cyclohexane that is optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl. In yet other embodiments where R_1 and R_5 are hydrogen, R_4 may also be hydrogen, and R_2 and R_3 may be independently selected from hydroxyl, trifluoromethyl, alkyl, amino, nitro, or aryl. In still other embodiments where R_1 and R_5 are hydrogen, R_2 , R_3 , and R_4 may also be hydrogen, and X may be alkylene or alkyleneamino. For example, X may be —(NH)—(CH₂)_n—, wherein n is 1-3.

Exemplary compounds according to formula (I) include:

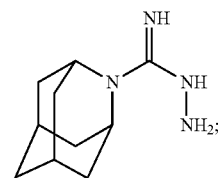
N-Adamantan-1-yl-guanidine;
N-(1-Adamantan-1-yl-ethyl)-guanidine;
O-Adamantan-1-yl-hydroxylamine;
5-Methyl-3H-imidazole-4-carbaldehyde O-adamantan-1-yl-oxime;
Adamantane-1-carboxamidine;
Adamantane amidine hydrochloride;
2,2-spiro adamantyl-1,3-dithian-5-aminium chloride;
N-Hydroxy-adamantane-1-carboxamidine;
4-Aza-tricyclo[4.3.1.1.3,8]undecane;
4-Azoniatricyclo[4.3.1.1.3,8]undecane chloride;



Adamantane-1-carbaldehyde;
Adamantan-2-ylamine;
Adamantane-2,6-dione;
2-Trifluoromethyl-adamantan-2-ol;
1-Nitro-adamantane;
2-Nitro-adamantane;
2-Methyl-adamantan-2-ol;
2-Methyl-adamantan-2-ylamine;
2-Methyl-2-nitro-adamantane;
2-Trifluoromethyl-adamantan-2-ylamine;
2-(4-amino-cyclohexyl)-adamantane;
2-(1H-Pyrazol-3-yl)-adamantan-2-ol;
2-Aza-tricyclo[3.3.1.1.3,7]decan-2-ol;
Adamantane-1-carboximidic acid methyl ester;
2-Aza-tricyclo[3.3.1.1.3,7]decane;
2-Aza-tricyclo[3.3.1.1.3,7]decan-2-ol;
2-Aza-tricyclo[3.3.1.1.3,7]dec-2-ylamine;
2-Aza-tricyclo[3.3.1.1.3,7]decane-2-carboxylic acid amide;
2-Aza-tricyclo[3.3.1.1.3,7]decane-2-carbothioic acid amide;
2-Aza-tricyclo[3.3.1.1.3,7]decane-2-carboxamidine;
2-Aza-tricyclo[3.3.1.1.3,7]decane-2-carboximidic acid methyl ester;

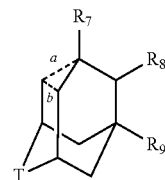
12

2-Aza-tricyclo[3.3.1.1.3,7]decane-2-carboximidothioic acid methyl ester;



2-Aza-tricyclo[3.3.1.1.3,7]decan-1-ol;
1-Chloro-2-aza-tricyclo[3.3.1.1.3,7]decane;
and a stereoisomer, partial stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, and N-oxide thereof.

In another aspect, provided are compounds having the formula (II):



wherein
dashed lines a and b independently represent optional bonds, wherein at least one of a and b must be present as a bond;

T is alkylene;
 R_7 is hydrogen, deuterium, halo, hydroxyl, nitro, guanidiny, -(alkylene)-guanidine, formamidinyl, carbonyl, oxime, amino, aminocarbonyl, aminooxy, aralkoxy, or aralkylaminooxy;

R_8 is hydrogen, deuterium, hydroxyl, carbonyl, amino, nitro, alkyl, trifluoromethyl, aryl, aminocarbonyl, or —NH—SO₂—NH₂; and,

R_9 is hydrogen, alkyl, hydroxyl, amino, nitro, aryl, guanidinyl, or -(alkylene)-guanidine;
or a stereoisomer, partial stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof.

With respect to the compounds according to formula (II), certain provisos may apply. These provisos may also optionally apply pursuant to the presently disclosed methods. For example, if T is ethylene, a is a bond, b is not a bond, R_7 is hydrogen, and R_8 is hydrogen, then R_9 cannot be -methylene-guanidine. Additionally, if T is ethylene or methylene, a is a bond, b is not a bond, R_8 is hydrogen, and R_9 is hydrogen, then R_7 cannot be amino. Furthermore, Additionally, if T is methylene, a is a bond, b is not a bond, R_7 is hydrogen, and R_9 is hydrogen, then R_8 cannot be amino or carbonyl. Additionally, if T is methylene, a is a bond, b is not a bond, R_8 is hydrogen, and R_9 is hydrogen, then R_7 cannot be —CH(NH³+Cl⁻)CH₂CH₃.

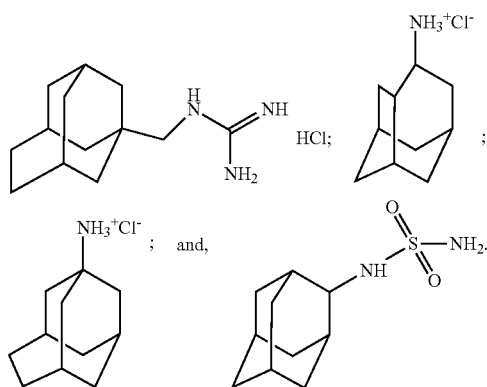
In some embodiments, R_7 is amino having the structure —NH³+Cl⁻. With respect to some of these embodiments, a may be present as a bond, and b is absent. In other instances, b is present as a bond, and a is absent. In other instances where R_7 is amino having the structure —NH³+Cl⁻, T is C₂-C₄ alkylene, with ethylene being one example. In other examples

13

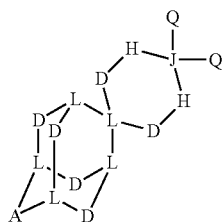
where R_7 is amino having the structure $-\text{NH}_3^+\text{Cl}^-$, one or both of R_8 and R_9 may be hydrogen.

In other embodiments of compounds according to formula (II), R_7 is hydrogen. When R_7 is hydrogen, R_8 may be hydrogen, deuterium, hydroxyl, carbonyl, amino, nitro, alkyl, trifluoromethyl, aryl, aminocarbonyl, or $-\text{NH}-\text{SO}_2-\text{NH}_2$. In one example wherein R_7 is hydrogen, R_8 is $-\text{NH}-\text{SO}_2-\text{NH}_2$. In other instances wherein R_7 is hydrogen, T is C_2 - C_4 alkylene, with ethylene being one example. Where R_7 is hydrogen, and T is C_2 - C_4 alkylene, R_8 may be hydrogen, deuterium, hydroxyl, carbonyl, amino, nitro, alkyl, trifluoromethyl, aryl, aminocarbonyl, or $-\text{NH}-\text{SO}_2-\text{NH}_2$; for example, R_8 may be hydrogen. Where R_7 is hydrogen, and T is C_2 - C_4 alkylene, R_9 may be hydrogen, alkyl, hydroxyl, amino, nitro, aryl, guanidiny, or $-(\text{alkylene})$ -guanidine; for example, R_9 may be $-(\text{alkylene})$ -guanidine, and, more particularly, may be $-(\text{C}_1$ - C_4 alkylene)-guanidine, such as $-\text{methylene-guanidine}$.

Exemplary compounds according to formula (II) include:



In yet another aspect, provided are compounds having the formula (III):



wherein

A and each D are independently $-(\text{CH}_2)_n-$, $-\text{S}(\text{O})_m-$, $(\text{CH}_2)_n-$, $-(\text{CH}_2)_n-\text{S}(\text{O})_m-$, $-\text{O}-(\text{CH}_2)_n-$, $-(\text{CH}_2)_n-\text{O}-$, $-\text{NH}-(\text{CH}_2)_n-$, $-(\text{CH}_2)_n-\text{NH}-$, or $-\text{NCH}_3-(\text{CH}_2)_n-$, wherein one or both hydrogens in a CH_2 group may independently be substituted with halogen or C_1 - C_6 alkyl, and wherein m and n are each independently 0-2, or,

A is a disubstituted quaternary carbon having substituents that are independently C_1 - C_6 alkyl optionally substituted with halogen, or that, along with A , together form a 3- to 7-member carbocyclic or heterocyclic ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl;

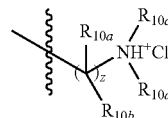
each H is independently $-(\text{CH}_2)_z-$, optionally substituted with halogen or C_1 - C_6 alkyl;

14

z is 0-3;

J is carbon or nitrogen;

each Q is independently hydrogen, alkyl, amino, hydroxyl, carbonyl, nitro, amidinyl, guanidiny, $-(\text{CH}_2)_z-\text{NH}_3^+\text{Cl}^-$, or



wherein each R_{10} is independently hydrogen or alkyl optionally substituted with halogen;

or,

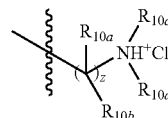
both Q substituents together along with J form a 3- to 7-member carbocyclic or heterocyclic ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl;

each L is independently carbon, nitrogen, or silicon, except that no more than two L substituents are chosen as nitrogen, and no more than two L substituents are chosen as silicon; or a stereoisomer, partial stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N -oxide thereof.

In some embodiments of the compounds according to formula (III), A , each D substituent, or both A and each D substituent are alkylene, for example $-(\text{CH}_2)_{1-6}-$. In certain instances, each D substituent is methylene or ethylene, and A is methylene or ethylene.

In other instances A is a bond (i.e., the atoms at the adjacent L positions are connected by a bond), and/or one or more D substituent is a bond. For example, if A is a bond, one or more D substituents may be a bond or may be alkylene, such as methylene or ethylene. In other examples, A is alkylene, and one or more D substituents may be a bond. For example, A may be methylene or ethylene, and one or both of the D substituents that are adjacent to the L substituent at the 2-position on the adamantane base structure may be a bond, or may be alkylene.

In certain embodiments of the compounds according to formula (III), a four- to seven-membered ring is bound to the L substituent at the 2-position on the adamantane base structure. When a four- to seven-membered ring may be present at the specified location, the ring may be carbocyclic or heterocyclic, and the Q substituents are independently hydrogen, alkyl, amino, hydroxyl, nitro, amidinyl, guanidiny, $-(\text{CH}_2)_z-\text{NH}_3^+\text{Cl}^-$, or



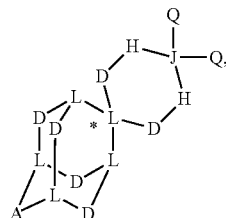
wherein each R_{10} is independently hydrogen or alkyl optionally substituted with halogen;

or,

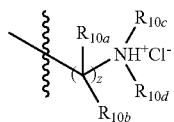
both Q substituents together along with J form a 3- to 7-member carbocyclic or heterocyclic ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl.

15

In some embodiments wherein a four- to seven-membered ring is bound to the L substituent at the 2-position on the adamantane base structure, i.e., at the position designated by an asterisk below:

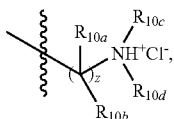


one Q substituent may be hydrogen. When one Q substituent is hydrogen under such conditions, the other Q substituent may be, for example,



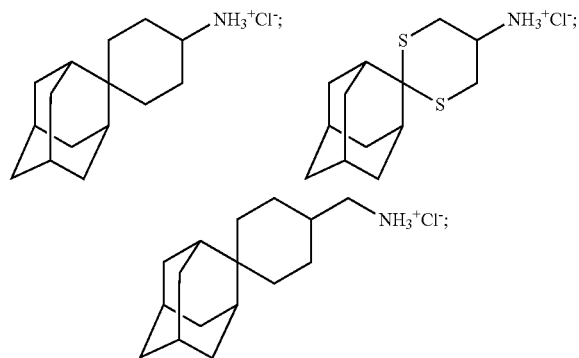
wherein each R_{10} is independently hydrogen or alkyl optionally substituted with halogen. In some instances, the other Q substituent may be $\text{—NH}_3^+\text{Cl}^-$, or may be $\text{—alkylene—NH}_3^+\text{Cl}^-$. For example, one Q substituent may be hydrogen, the other Q substituent may be $\text{—NH}_3^+\text{Cl}^-$, or may be $\text{—alkylene—NH}_3^+\text{Cl}^-$, and A, each D substituent, or both A and each D substituent may be alkylene, for example $\text{—(CH}_2\text{)}_{1-6}\text{—}$.

In certain embodiments wherein one Q substituent is

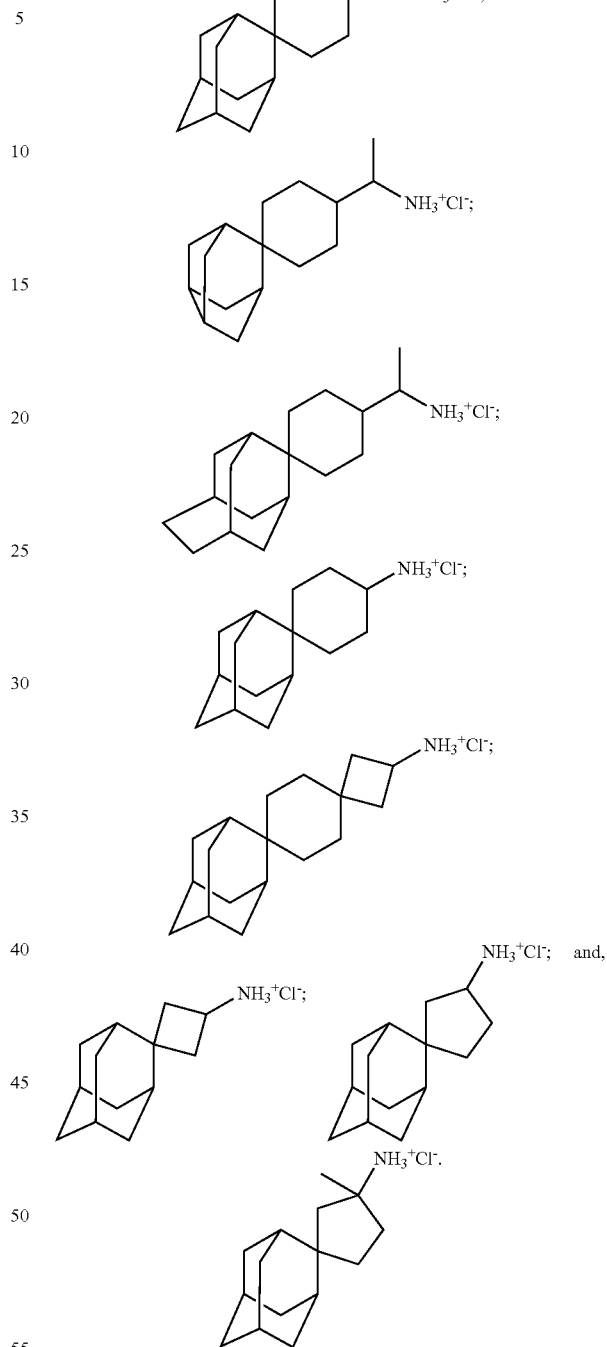


z may be 0 or 1, and one or both of R_{10c} and R_{10d} may be hydrogen. Under such circumstances, one or both of R_{10a} and R_{10b} may be alkyl.

Exemplary compounds according to formula (III) include:

**16**

-continued



The compounds employed in the present invention may exist in prodrug form. As used herein, “prodrug” is intended to include any covalently bonded carriers which release the active parent drug, for example, as according to the formulas or compounds employed in the methods of the present invention in vivo when such prodrug is administered to a subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may, if desired, be delivered in prodrug form. Thus, the present invention contemplates methods of delivering pro-

drugs. Prodrugs of the compounds employed in the present invention, for example, according to formula (I), may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound.

Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or carboxylic acid, respectively. Examples include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups; and alkyl, carbocyclic, aryl, and alkylaryl esters such as methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, phenyl, benzyl, and phenethyl esters, and the like.

As will be readily understood, functional groups present may contain protecting groups during the course of synthesis. Protecting groups are known per se as chemical functional groups that can be selectively appended to and removed from functionalities, such as hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound is exposed. Any of a variety of protecting groups may be employed with the present invention. Protecting groups that may be employed in accordance with the present invention may be described in Greene, T. W. and Wuts, P. G. M., *Protective Groups in Organic Synthesis 2d. Ed.*, Wiley & Sons, 1991.

In a further aspect, the invention relates to pharmaceutical compositions comprising a compound according to formula (I) and a pharmaceutically acceptable carrier, diluent, or excipient. The applicable carrier, diluent, or excipient may be selected on the basis of the chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, Pa., 1985), the disclosure of which is hereby incorporated by reference in its entirety.

Also provided are methods for treating an influenza A virus-affected disease state or infection comprising the step of administering to a subject in need thereof a composition comprising a compound of formula (I), a compound of formula (II), a compound of formula (III), or any combination thereof, wherein the compounds of formulas (I), (II), and (III) are defined as previously specified, and a pharmaceutically acceptable carrier, diluent, or excipient.

The influenza A virus-affected disease state or infection may comprise any condition that arises as a direct or indirect result of the presence of influenza A virus. For example, the influenza A virus-affected disease state may comprise influenza (flu), pneumonia, bronchitis, sinus infection, or ear infection, among other conditions. The disease state or infection may arise as a direct or indirect result of the presence of wild-type influenza A virus, or may arise as a direct or indirect result of the presence of a mutant version of the influenza A virus, or may arise as a direct or indirect result of the presence of both a wild-type influenza A virus and a mutant version of the influenza A virus. Thus, in accordance with the present methods, the influenza A virus may be wild-type or may be a mutant virus. The mutant virus may comprise an influenza A virus having the V27G mutation, the V27I mutation, the V27T mutation, the V27S mutation, or the V27A mutation; may comprise an influenza virus having the A30T mutation; may comprise an influenza virus having the S31A mutation or the S31N mutation; may an influenza virus having the G34E mutation or the G34A mutation; may comprise an influenza virus having the W41L mutation or the W41Y mutation; may

comprise an influenza virus having the D44N mutation or the D44H mutation; and/or may comprise an influenza virus having the R45K mutation or the R45H mutation.

The compounds of this invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers, diluents, or excipients, which may be liquid or solid. The applicable solid carrier, diluent, or excipient may function as, among other things, a binder, disintegrant, filler, lubricant, glidant, compression aid, processing aid, color, sweetener, preservative, suspending/dispersing agent, tablet-disintegrating agent, encapsulating material, film former or coating, flavors, or printing ink. Of course, any material used in preparing any dosage unit form is preferably pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations. Parenteral administration in this respect includes administration by, inter alia, the following routes: intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, transepithelial including transdermal, ophthalmic, sublingual and buccal; topically including ophthalmic, dermal, ocular, rectal and nasal inhalation via insufflation, aerosol, and rectal systemic.

In powders, the carrier, diluent, or excipient may be a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier, diluent or excipient having the necessary compression properties in suitable proportions and compacted in the shape and size desired. For oral therapeutic administration, the active compound may be incorporated with the carrier, diluent, or excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The amount of active compound(s) in such therapeutically useful compositions is preferably such that a suitable dosage will be obtained. The therapeutic compositions preferably contain up to about 99% of the active ingredient.

Liquid carriers, diluents, or excipients may be used in preparing solutions, suspensions, emulsions, syrups, elixirs, and the like. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid such as water, an organic solvent, a mixture of both, or pharmaceutically acceptable oils or fat. The liquid carrier, excipient, or diluent can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, or osmo-regulators.

Suitable solid carriers, diluents, and excipients may include, for example, calcium phosphate, silicon dioxide, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, ethylcellulose, sodium carboxymethyl cellulose, microcrystalline cellulose, polyvinylpyrrolidone, low melting waxes, ion exchange resins, croscarmellose carbon, acacia, pregelatinized starch, crospovidone, HPMC, povidone, titanium dioxide, polycrystalline cellulose, aluminum methahydroxide, agar-agar, tragacanth, or mixtures thereof.

Suitable examples of liquid carriers, diluents and excipients for oral and parenteral administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil), or mixtures thereof.

For parenteral administration, the carrier, diluent, or excipient can also be an oily ester such as ethyl oleate and

isopropyl myristate. Also contemplated are sterile liquid carriers, diluents, or excipients, which are used in sterile liquid form compositions for parenteral administration. Solutions of the active compounds as free bases or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. A dispersion can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include, for example, sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form is preferably sterile and fluid to provide easy syringability. It is preferably stable under the conditions of manufacture and storage and is preferably preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier, diluent, or excipient may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of a dispersion, and by the use of surfactants. The prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions may be achieved by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions may be prepared by incorporating the active compounds in the required amounts, in the appropriate solvent, with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions may be prepared by incorporating the sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation may include vacuum drying and the freeze drying technique that yields a powder of the active ingredient or ingredients, plus any additional desired ingredient from the previously sterile-filtered solution thereof.

The compounds of the invention may be administered in an effective amount by any of the conventional techniques well-established in the medical field. The compounds employed in the methods of the present invention including, for example, the compounds of formula I may be administered by any means that results in the contact of the active agents with the agents' site or sites of action in the body of a patient. The compounds may be administered by any conventional means available.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets, buccal tablets, troches, capsules, elixirs, powders, solutions, suspensions, emulsions, syrups, wafers, granules, suppositories, or the like. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. In addition, dosage forms of

the present invention can be in the form of capsules wherein one active ingredient is compressed into a tablet or in the form of a plurality of microtablets, particles, granules or non-perils. These microtablets, particles, granules or non-perils are then placed into a capsule or compressed into a capsule, possibly along with a granulation of the another active ingredient.

The dosage of the compounds of the present invention that will be most suitable for prophylaxis or treatment will vary with the form of administration, the particular compound chosen and the physiological characteristics of the particular patient under treatment. Generally, small dosages may be used initially and, if necessary, increased by small increments until the desired effect under the circumstances is reached. Generally speaking, oral administration may require higher dosages.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The dose may also be provided by controlled release of the compound, by techniques well known to those in the art.

The compounds useful in the methods of the present invention may be prepared in a number of ways well known to those skilled in the art. The compounds can be synthesized, for example, by the methods as described below, or variations thereon as appreciated by the skilled artisan. The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature. All processes disclosed in association with the present invention are contemplated to be practiced on any scale, including milligram, gram, multigram, kilogram, multikilogram or commercial industrial scale.

The present invention is further defined in the following Examples. It should be understood that these examples, while indicating preferred embodiments of the invention, are given by way of illustration only, and should not be construed as limiting the appended claims. From the above discussion and these examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

EXAMPLES

All chemicals for use in preparing the inventive compounds were purchased from commercial vendors and used without further purification, unless otherwise noted.

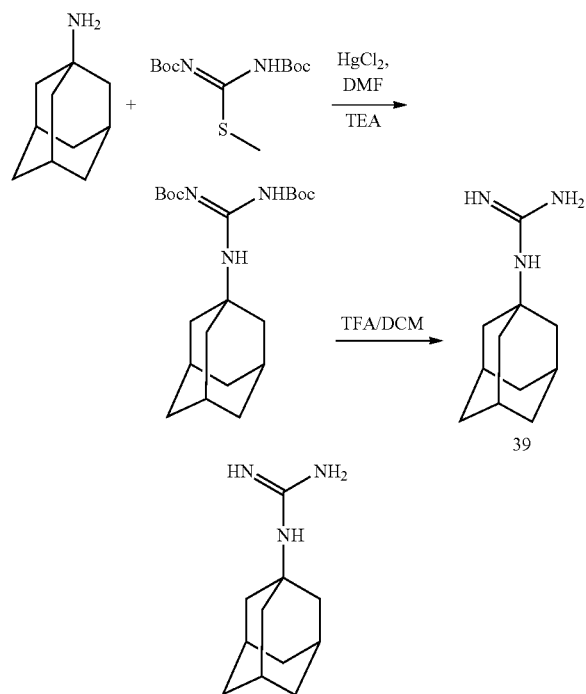
Example 1

Synthesis of and NMR/Mass Spectrometry Data for Exemplary Influenza A M2 Proton Channel Inhibitors

Synthesis of some preferred embodiments was accomplished as illustrated in the following generalized schematics and as described below:

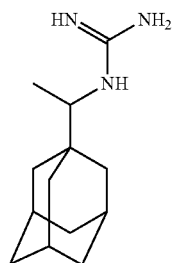
Compounds 38, 41 were purchased from ChemBridge Co; Compounds 48, 50, 51 were purchased from Aldrich Co and used without further purification.

21



1-(adamantyl)guanidine (39)

Amantadine (0.30 g, 2 mmol), HgCl_2 (0.54 g, 2 mmol), and 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea (0.58 g, 2 mmol) were stirred in DMF (10 mL) under a N_2 atmosphere for 24 h. H_2O was added to the reaction mixture, and the white precipitate was removed by filtration. The precipitate was washed with CH_2Cl_2 twice, and the combined filtrate was extracted with CH_2Cl_2 , washed with brine and dried over MgSO_4 , concentrated in vacuo, and purified by flash chromatography. The Boc protecting group was removed by 50% TFA/ CH_2Cl_2 for 2 h at RT. Excess TFA was removed by passing N_2 through the solution to give a yellow solid which was subsequently purified by flash chromatography (0.41 g, 74% over two steps). $^1\text{H-NMR}$ (360 MHz, CD_3OD) δ 2.13 (br s, 3H), 1.97 (br s, 6H), 1.76 (br s, 6H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 160.35, 53.83, 42.45, 36.86, 31.03; ESI-MS: Calculated for $\text{C}_{11}\text{H}_{19}\text{N}_3$ ($\text{M}+\text{H}$) $^+$ 194.2. Found: 194.7.

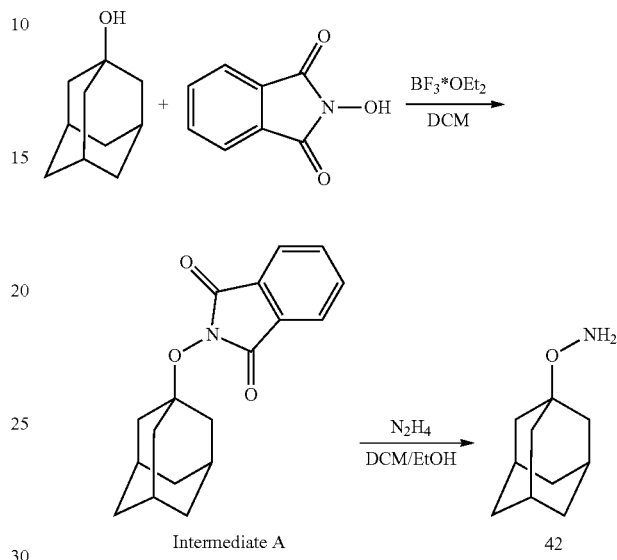


1-(1-adamantylethyl)guanidine (40)

Compound 40 was synthesized according to the same procedure as described for compound 39. $^1\text{H-NMR}$ (360 MHz,

22

CD_3OD) δ 3.20 (dd, $J=13.32$ Hz, 6.84 Hz, 1H); 2.01 (br s, 3H), 1.80-1.76 (m, 3H), 1.71-1.67 (m, 3H), 1.59 (br s, 6H), 1.14 (d, $J=6.84$ Hz); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 159.3, 57.86, 39.25, 38.10, 29.89, 14.65; ESI-MS: Calculated for $\text{C}_{13}\text{H}_{23}\text{N}_3$ ($\text{M}+\text{H}$) $^+$ 222.3. Found: 222.3.

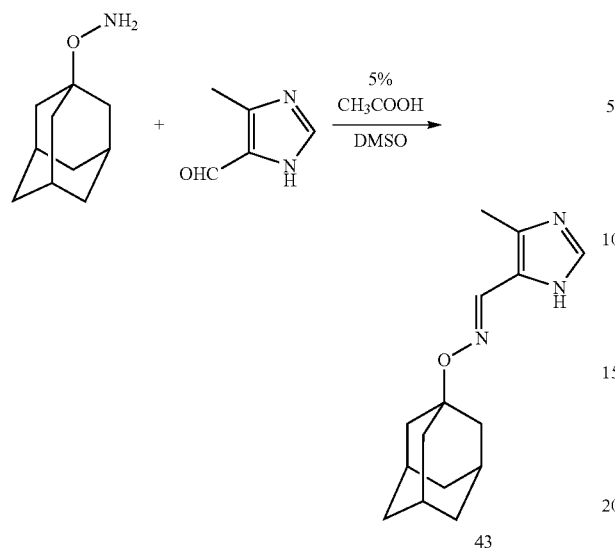


O-adamantylhydroxylamine (42) (see Palandoken, H.; Bocian, C. M.; McCombs, M. R.; Nantz, M. H. *Tetrahedron Letters* 2005, 46, 6667-6669)

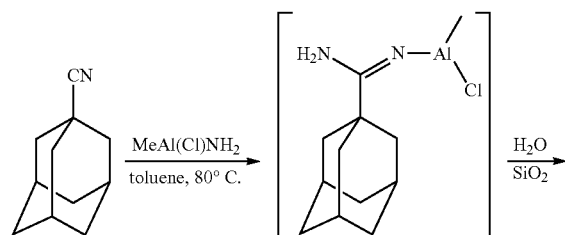
Intermediate A. To a solution of 1-adamantol (6.08 g, 40 mmol), N-hydroxy-phthalimide (6.53 g, 40 mmol) in 50 ml DCM at 0°C . was added $\text{BF}_3 \cdot \text{OEt}_2$ (5.02 ml, 40 mmol) under N_2 atmosphere, the resulting solution was allowed to warm to room temperature and stirred overnight. Solvent was removed in vacuo and the crude mixture was purified by flash column chromatography (DCM) to give O-adamantyl phthalimide (9.28 g, Yield 78%) as white solid. $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 7.85-7.81 (m, 2H), 7.77-7.74 (m, 2H), 2.27 (br s, 3H), 1.97 (br s, 6H), 1.69 (br s, 6H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 166.78, 134.49, 129.45, 123.53, 85.70, 41.22, 36.06, 31.13; ESI-MS: Calculated for $\text{C}_{18}\text{H}_{19}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$ 298.4. Found: 298.4.

To a solution of O-adamantyl phthalimide (2.97 g, 10 mmol) in DCM/EtOH (v/v 1:5) was added hydrazine (3.2 ml, 100 mmol), the resulting solution was stirred at ambient temperature for 4 hrs. Solvent was removed in vacuo and the desired product was separated as white solid (1.42 g, Yield: 85%) by flash column chromatography (DCM to 8% MeOH/DCM). $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 4.81 (br s, 2H), 2.15 (brs, 3H), 1.76 (brs, 6H), 1.59 (brs, 6H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 76.11, 40.55, 36.76, 30.67; ESI-MS: Calculated for $\text{C}_{10}\text{H}_{17}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 168.3. Found: 168.4.

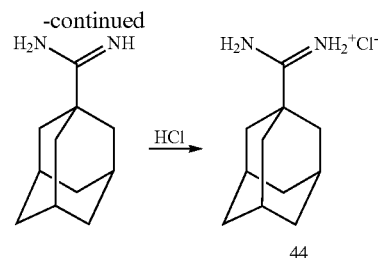
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To a solution of O-adamantylhydroxylamine (0.17 g, 1 mmol) and 4-methyl-1H-imidazole-5-carbaldehyde (0.11 g, 1 mmol) in 5 ml anhydrous DMSO was added 3 μl CH_3COOH . The resulting mixture was stirred at ambient temperature overnight. H_2O (40 ml) was added and the mixture was lyophilized to give white solid. (0.25 g, Yield: 96%). $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 8.08 (s, 1H), 7.55 (s, 1H), 2.31 (s, 3H), 2.18 (br s, 3H), 1.88 (br s, 6H), 1.63 (br s, 6H); $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ 138.5, 138.3, 135.22, 78.16, 41.79, 36.65, 30.84, 12.10; ESI-MS: Calculated for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}$ ($\text{M}+\text{H}$) $^+$ 260.4. Found: 260.2.

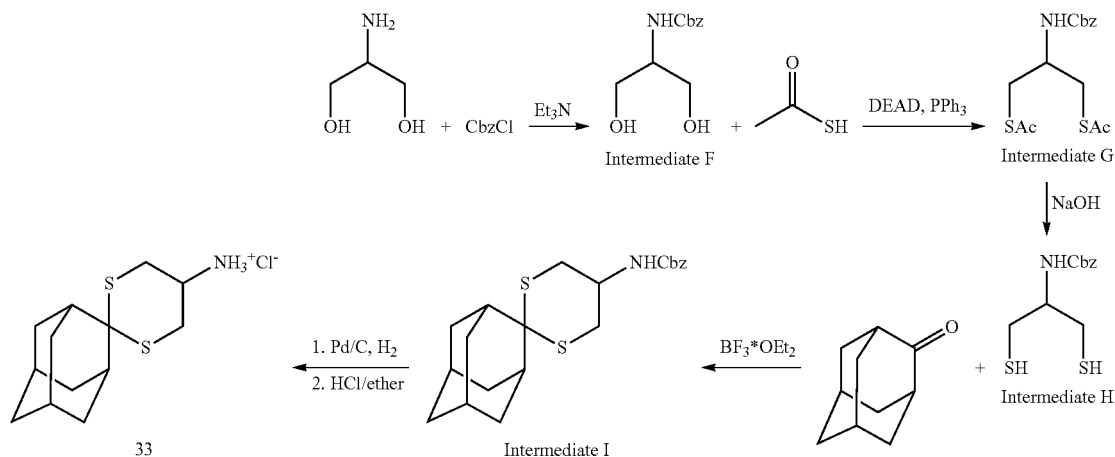


24



Adamantane amidine hydrochloride (44) (see Moss, R. A.; Ma, W; Merrer, D. C.; Xue, S. *Tetrahedron Letters* 1995, 36, 8761-8764)

A 2M Me_3Al (25 ml, 50 mmol) in toluene was added dropwise to a solution of NH_4Cl (2.9 g, 54 mmol) in anhydrous toluene at 5°C . under a N_2 atmosphere. The mixture was allowed to warm to ambient temperature and stirred for 2 hrs. Then, a solution of adamantane carbonitrile (4.83, 30 mmol) in 10 ml of anhydrous toluene was added and the solution was heated to 80°C . for 18 hrs under N_2 . The reaction mixture was slowly poured into a slurry of 15 g of silica gel in 50 ml of CHCl_3 and stirred for 5 mins. The silica was filtered and washed with MeOH. The filtrate was concentrated in vacuo to a residue of 15 ml which was refiltered to remove NH_4Cl . Then, 10 ml of methanolic HCl (2 ml, 54 mmol) was added to the filtrate, followed by 400 ml ether. The white precipitation formed after 10 hrs of stirring was filtrated. The crude white solid was added to 150 ml of 4:1 v/v isopropanol/acetone and stirred at ambient temperature for 12 hrs. The mixture was filtrated to remove undissolved NH_4Cl , the filtrate was concentrated to 15 ml, and 300 ml of ether was added. The white precipitate was filtered and dried in vacuum to give 44 as white solid (3.67 g, Yield: 58%). $^1\text{H-NMR}$ (360 MHz, CD_3OD) δ 2.04 (br s, 6H), 1.96 (br s, 3H), 1.79 (br s, 6H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 131.94, 50.00, 41.04, 36.80, 28.69; ESI-MS: Calculated for $\text{C}_{11}\text{H}_{18}\text{N}_2$ ($\text{M}+\text{H}$) $^+$ 179.3. Found: 179.6.



25

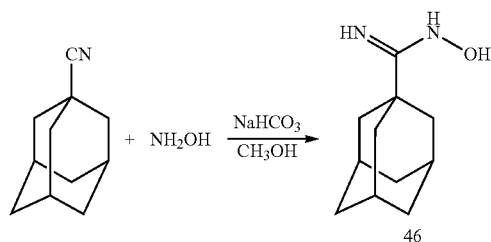
Intermediate H was synthesized from serinol following the procedure as described in WO9922735-A; WO9922735-A1; AU9912854-A; and, U.S. Pat. No. 6,117,880-A.

Benzyl 2,2-spiro
adamantyl-1,3-dithian-5-ylcarbamate (Intermediate
I)

To a solution of 2-adamantone (1.27 g, 5 mmol) and intermediate H (0.74 g, 5 mmol) in 10 ml degassed DCM was added $\text{BF}_3 \cdot \text{OEt}_2$ at 0°C . under a N_2 atmosphere. The resulting mixture was allowed to warm to ambient temperature and stirred overnight. Saturated NaHCO_3 was added to the mixture and extracted with DCM for 3 times. The combined organic layer was washed with brine, dried over anhydrous MgSO_4 , filtrated and concentrated in vacuum. The crude product was purified by flash chromatography (15% to 30% EA/Hexane) to give Intermediate I as white solid. (1.46 g, Yield: 75%). $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 7.35-7.29 (m, 5H), 5.08 (s, 2H), 3.84-3.81 (m, 1H), 2.94 (dd, $J=14.3$ Hz, 3.35 Hz, 2H), 2.77 (dd, $J=14.3$ Hz, 7.76 Hz, 2H), 2.49 (t, $J=15.8$ Hz, 4H), 2.30 (d, $J=15.8$ Hz, 2H), 1.83 (s, 2H), 1.76 (s, 2H), 1.70 (s, 2H), 1.66 (s, 2H); $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ 129.63, 129.12, 129.00, 67.74, 45.79, 39.94, 37.12, 37.00, 34.33, 34.04, 31.05, 29.07; ESI-MS: Calculated for $\text{C}_{21}\text{H}_{27}\text{NO}_2\text{S}_2$ (M+H) $^+$ 390.6. Found: 390.6.

2,2-spiro adamantyl-1,3-dithian-5-aminium chloride
(33)

To a solution of intermediate I (0.39 g, 1 mmol) in CH_3OH was added 10% Pd/C (50 mg) and NH_4CHO (1.00 g), the resulting mixture was charged with H_2 balloon and stirred overnight. The mixture was filtrated and washed with CH_3OH ; 2 ml of 4M HCl in dioxane was added to convert amine to ammonium chloride salt. Solvent was removed in vacuum, and the crude product was purified by flash chromatography (5%-15% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give 33 as yellow solid (0.24 g, Yield: 85%). $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 3.65-3.38 (m, 1H), 3.34 (dd, $J=15.2$ Hz, 5.5 Hz, 2H), 2.82 (dd, $J=15.2$ Hz, 5.5 Hz, 2H), 2.54-2.44 (m, 6H), 1.78-1.68 (m, 8H); $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ 42.94, 39.74, 38.71, 34.11, 33.70, 29.17, 28.97; ESI-MS: Calculated for $\text{C}_{13}\text{H}_{22}\text{CINS}_2$ (M+H) $^+$ 292.9. Found: 292.7.

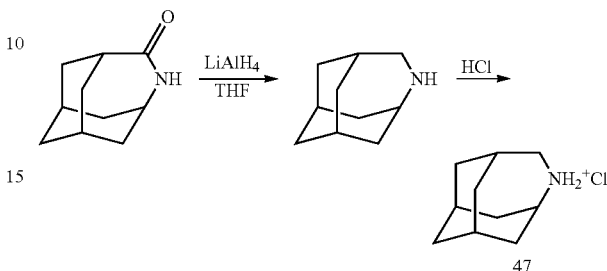


N-hydroxyadamantanecarboximidamide (46)

A suspension of 1-nitrile adamantane (0.96 g, 6 mmol), hydroxylamine hydrochloride (0.5 g, 7.2 mmol) and NaHCO_3 (0.60 g, 7.2 mmol) in CH_3OH (15 ml) was refluxed for 4 hrs, and then concentrated in vacuo to remove CH_3OH . The residue was extracted with ethyl acetate, washed with brine and dried over MgSO_4 to afford crude mixture, which was subsequently purified by flash chromatography (5%-

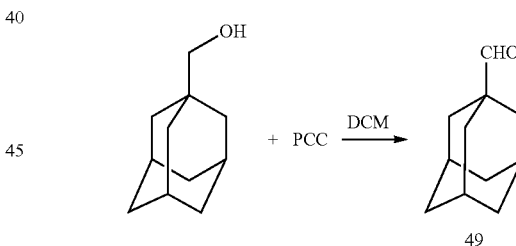
26

15% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give 46 as white solid (0.84 g, Yield: 72%). $^1\text{H-NMR}$ (360 MHz, CD_3OD) δ 2.05 (br s, 4H), 2.01 (br s, 3H), 1.86-1.84 (m, 2H), 1.80-1.74 (m, 6H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 41.09, 40.87, 37.92, 36.88, 29.88, 28.78; ESI-MS: Calculated for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}$ (M+H) $^+$ 195.3. Found: 195.7.



4-Azatricyclo[4.3.1.1^{3,8}]undecan hydrochloride (47)

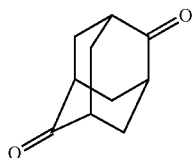
To a solution of 4-Azatricyclo[4.3.1.1^{3,8}]undecan-5-one (1.65 g, 10 mmol) in anhydrous THF was added LiAlH_4 (1.5 g) protonwise over 10 mins at 0°C . The resulting slurry was heated to reflux for 6 hrs. H_2O (1.5 ml), 15% NaOH (1.5 ml) and H_2O (4.5 ml) were sequentially added to the mixture and stirred for half hour before filtration. The filtrate was concentrated and 2 ml of 4M HCl in dioxane was added, the mixture was concentrated again and purified by flash chromatography (CH_2Cl_2 to 15% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give 47 as white solid. (1.60 g, Yield: 85%). $^1\text{H-NMR}$ (360 MHz, CD_3OD) δ 2.80-2.77 (m, 3H), 1.83 (br s, 1H), 1.61-1.52 (m, 6H), 1.36-1.31 (m, 2H), 1.71-1.36 (m, 4H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 53.72, 52.61, 37.17, 34.98, 34.87, 32.09, 27.27; ESI-MS: Calculated for $\text{C}_{10}\text{H}_{17}\text{N}$ (M+H) $^+$ 152.3. Found: 152.4.



1-adamantanecarbaldehyde (49)

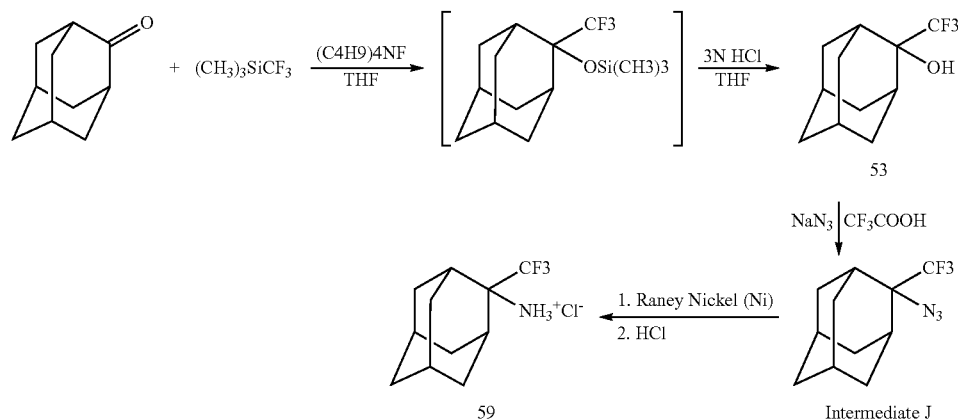
To a solution of 1-adamantanemethanol (1.66 g, 10 mmol) in CH_2Cl_2 was added PCC (4.3 g, 20 mmol) at 0°C . The resulting mixture was stirred at the same temperature for 10 mins before warming to ambient temperature. Stirring was continued for 1.5 hrs until the disappearance of starting material as checked by TLC. Water was added and extracted with CH_2Cl_2 for 3 times. The combined organic phase was dried over MgSO_4 , filtrated and concentrated in vacuo. The crude mixture was separated by flash chromatography (50%-100% $\text{CH}_2\text{Cl}_2/\text{Hexane}$) to give 49 as white solid (1.36 g, Yield: 83%). $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 9.32 (s, 1H), 2.07 (br s, 3H), 1.77 (br s, 6H), 1.72 (br s, 6H); $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ 206.07, 45.03, 37.25, 36.10, 27.61; ESI-MS: Calculated for $\text{C}_{11}\text{H}_{16}\text{O}$ (M+H) $^+$ 165.2. Found: 165.5.

27



2,6-diadamantone (52)

Compound 52 was synthesized according to the procedure reported in Geluk, H. W.; Schlatma. *J1 Recueil Des Travaux Chimiques Des Pays-Bas* 1971, 90, 516-&.



2-trifluoromethyl-2-adamantol (53) (see Ramaiah, P.; Krishnamurti, R.; Prakash, G. K. S., *1-Trifluoromethyl-1-Cyclohexanol-(Cyclohexanol, 1-(Trifluoromethyl))*. In *Organic Syntheses*, Vol 72, 1995; Vol. 72, pp 232-240)

To a solution of $(\text{CH}_3)_3\text{SiCF}_3$ (1.92 g, 13 mmol) in anhydrous THF (10 ml) was added 2-adamantone (1.56 g, 10.4 mmol) in THF at 0°C . under a N_2 atmosphere, this is followed by addition of $(\text{C}_4\text{H}_9)_4\text{NF}$ (4 mg). The reaction mixture was stirred for another 30 mins and brought to ambient temperature for another 1 hr. To this reaction mixture were added THF (3 ml) and 3N HCl (4 ml). Stirring was continued for another 8 hrs and extracted with ether for 3 times. The combined ether layer was dried over MgSO_4 . The solvent was removed in vacuo and the residue was purified by flash column chromatography (CH_2Cl_2 to 5% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give 53 as waxy white solid (1.65 g, Yield: 72%). $^1\text{H-NMR}$ (360 MHz, CD_3OD) δ 2.33-2.30 (m, 2H), 2.12-2.04 (m, 4H), 1.84-1.78 (br s, 6H), 1.62-1.58 (m, 2H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 130.62, 39.67, 34.44, 33.76, 28.72, 27.99; ESI-MS: Calculated for $\text{C}_{11}\text{H}_{15}\text{F}_3\text{O}$ ($\text{M}+\text{H}$) $^+$ 221.2. Found: 221.5.

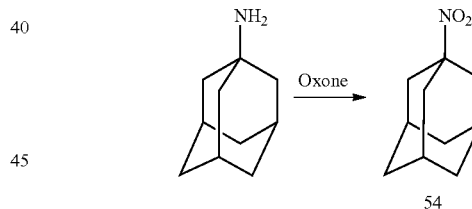
2-trifluoromethyl-2-adamantanemethanone (59) (see Kalir, A.; Balderman, D. *Organic Syntheses* 1981, 60, 104-108)

To a mixture of NaN_3 (1.3 g, 20 mmol) in chloroform at 0°C . were added CF_3COOH (3.75 ml, 50 mmol) and 2-trifluoromethyl-2-adamantanemethanol (2.20 g, 10 mmol). The resulting slurry was stirred at 0°C . for 4 hrs and then brought to room temperature with continuous stirring for overnight.

28

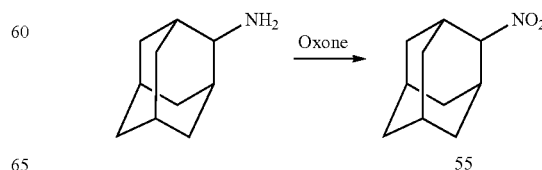
The mixture is cautiously neutralized with 15% aqueous ammonia solution and extracted with CHCl_3 for 3 times. The combined CHCl_3 was dried over MgSO_4 and concentrated in vacuo. The crude oily residue was dissolved in 2-propanol (10 ml) and heated to 70°C ., wet Raney nickel (2 g) was added. The mixture was heated for another 10 mins and filtrated, washed with 2-propanol. The combined filtrate was concentrated in vacuo and treated with 4 ml of 4M HCl in dioxane. Solvent was removed and the crude residue was separated by flash column chromatography (5% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ to 20% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give 59 as white solid (2.30 g, Yield: 90%). $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 2.28-2.24 (m, 2H), 2.12-2.09 (m, 4H), 1.99 (s, 1H), 1.88-1.84 (m, 2H), 1.78-1.75 (m, 4H), 1.63-1.60 (m, 2H); $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ

128.91, 38.48, 33.47, 32.72, 27.13, 26.42; ESI-MS: Calculated for $\text{C}_{11}\text{H}_{15}\text{F}_3\text{O}$ ($\text{M}-\text{NH}_2$) $^+$ 203.2. Found: 203.2



1-nitroadamantane (54)

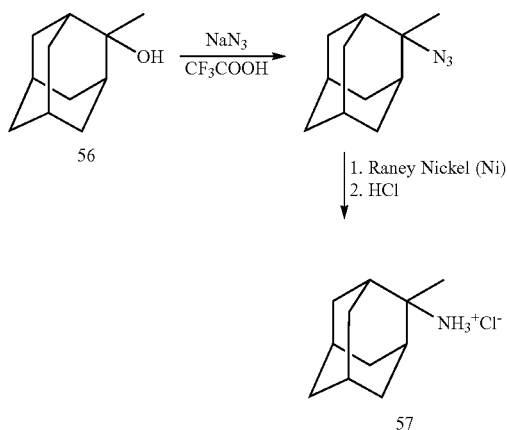
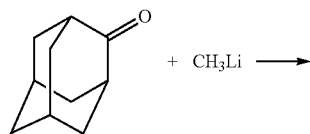
1-nitroadamantane was synthesized as reported in Braslau, R.; O'Bryan, G.; Nilsen, A.; Henise, J.; Thongpaisanwong, T.; Murphy, E.; Mueller, L.; Ruehl, J. *Synthesis-Stuttgart* 2005, 1496-1506.



29

2-nitroadamantane (55)

2-nitroadamantane was synthesized according to the procedure as described for 54. $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 3.42 (s, 1H), 2.54 (s, 2H), 1.97-1.92 (m, 4H), 1.91-1.96 (m, 2H), 1.82 (s, 4H), 1.48-1.44 (m, 2H); $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ 83.99, 37.48, 37.23, 32.46, 30.72, 27.31, 26.87; ESI-MS: Calculated for $\text{C}_{10}\text{H}_{15}\text{NO}_2$ (M-NO_2) $^+$ 135.1. Found: 135.1.



2-methyl-2-adamantol (56)

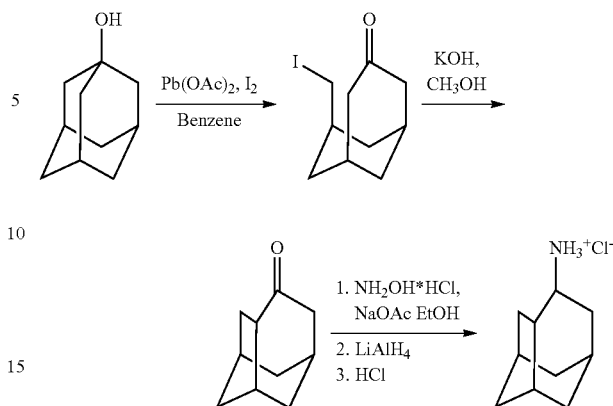
To a solution of 2-adamantone (1.50 g, 10 mmol) in ether was added CH_3Li (7.5 ml, 1.6M in ether, 12 mmol) dropwise at 0°C . under a N_2 atmosphere. The mixture was stirred for another hr at 0°C ., then brought to ambient temperature and stirred overnight. Saturated NH_4Cl solution was added and extracted with ether for three times. The combined ether was dried over MgSO_4 and concentrated in vacuo. The crude residue was separated by flash column chromatography (CH_2Cl_2 to 5% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give 56 as white solid (1.58 g, 95%). $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 2.20-2.16 (m, 2H), 1.89-1.75 (m, 6H), 1.68 (br s, 4H), 1.57-1.54 (m, 2H), 1.48 (br s, 1H), 1.35 (s, 3H); $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ 74.06, 39.30, 38.49, 35.33, 33.16, 27.73, 27.60, 27.22; ESI-MS: Calculated for $\text{C}_{11}\text{H}_{18}\text{O}$ (M+H) $^+$ 167.3. Found: 167.3.

2-methyl-2-adamantaneammonium chloride (57)

Compound 57 was synthesized according to the same procedure as described for compound 59.

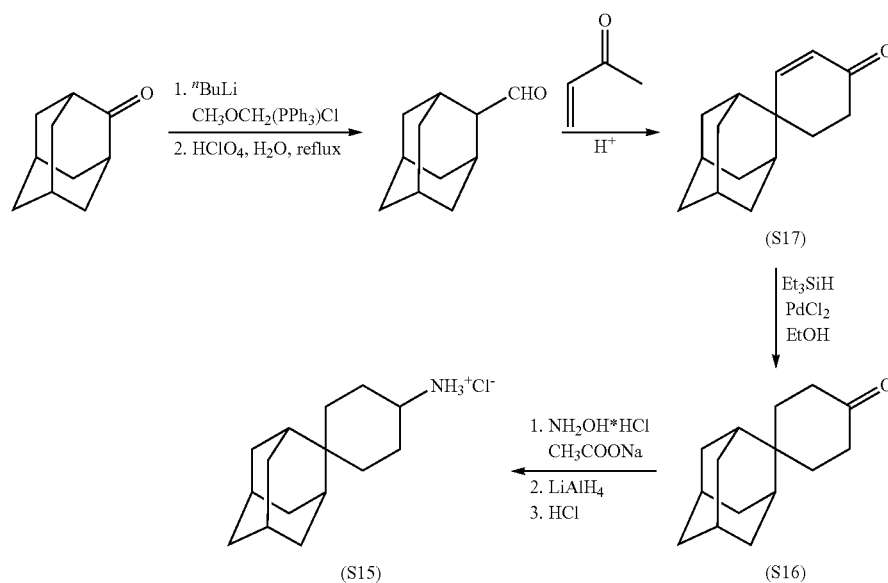
Compound S1 ((2S,3aS,5R)-octahydro-1H-2,5-methanoin-7-aminium chloride Protoadamantone) was synthesized via protoadamantone, which was made according to literature reported procedure. (Organic Syntheses, Vol. 59, p. 147 (1979))

30



Compound S1 (2S,3aS,5R)-octahydro-1H-2,5-methanoin-7-aminium chloride Protoadamantone was synthesized according to the literature procedure. It was converted to amine via two-step oxime formation and reduction to give compound S1 as yellow solid (65% Yield, exo/endo mixture). $^1\text{H-NMR}$ (360 MHz, CD_3OD) δ 3.64-3.45 (m, 1H), 2.53-1.46 (m, 14H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 50.92, 43.65, 42.29, 40.42, 39.97, 39.31, 38.32, 36.70, 36.36, 36.18, 34.20, 33.75, 33.02, 32.68, 32.33, 32.15, 29.63, 28.46; ESI-MS: Calculated for $\text{C}_{10}\text{H}_{17}\text{N}$ (M+H) $^+$ 152.3. Found: 152.3.

Compound S2 (tricyclo[4.3.1.1^{3,8}]undecan-1-aminium chloride) was synthesized from Tricyclo[4.3.1.1^{3,8}]undecane-1-carboxylic acid (Matrix Scientific Cat. No. #037551) using curtius rearrangement according to the procedure described in previous report. (Nasr, K., Pannier, N., Frangioni, J. V. & Maison, W. Rigid multivalent scaffolds based on adamantane. *J. Org. Chem.* 73, 1056-1060 (2008). Diphenylphosphorylazide (DPPA) (1.29 ml, 6 mmol) and triethylamine (0.84 ml, 6 mmol) were added to a solution of Tricyclo[4.3.1.1^{3,8}]undecane-1-carboxylic acid (0.97 g, 5 mmol) in 10 ml CH_2Cl_2 at ambient temperature. The reaction was stirred for 2 hours. An additional 10 ml CH_2Cl_2 and 10 ml H_2O were added to the reaction mixture, the organic layer was separated and washed sequentially with H_2O , saturated NaHCO_3 and brine and dried over MgSO_4 . Solvent was removed by rotary evaporation and t-BuOH (50 ml) was added. The solution was heated to reflux under N_2 atmosphere for 5 hours. Excess t-BuOH was removed in vacuo and the residue was treated with 50% TFA/ CH_2Cl_2 at ambient temperature for 2 hours. N_2 was purged through the mixture to remove excess TFA and CH_2Cl_2 to give yellow oil. 4M HCl in dioxane (3 ml) was added and the mixture was added dropwise to cold diethyl ether. A white solid was collected by centrifugation and subsequent decanting of the ether supernatant. Further flash column chromatography purification gave tricyclo[4.3.1.1^{3,8}]undecan-1-aminium chloride (compound S2) as a white solid (0.76 g, Yield: 75%). $^1\text{H-NMR}$ (360 MHz, CD_3OD) δ 2.28-2.24 (m, 3H), 1.96-1.93 (m, 4H), 1.90-1.87 (m, 4H), 1.82-1.72 (m, 4H), 1.55-1.52 (m, 2H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 53.91, 43.16, 42.46, 40.72, 38.18, 37.36, 35.87, 33.76, 32.54, 30.98, 28.38; ESI-MS: Calculated for $\text{C}_{11}\text{H}_{19}\text{N}$ (M+H) $^+$ 166.3. Found: 166.3.



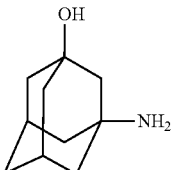
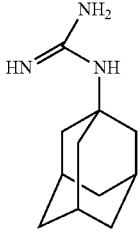
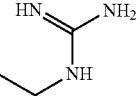
S15 was synthesized from 2-adamantone in two steps according to literature procedures. It was first converted to vinyl ether by witting reaction, and then followed by acid hydrolysis. Due to its instability, the aldehyde was used immediately for the next step robinson annelation reaction. The subsequent enone reduction and amination steps were performed as described above. S17 ((1r,3r,5r,7r)-spiro[adamantane-2,1'-cyclohex[2]en]-4'-one) $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 7.50 (d, $J=10.8$ Hz, 2H), 5.92 (d, $J=10.8$ Hz, 2H), 2.43 (t, $J=6.48$ Hz, 2H), 2.14-2.09 (m, 6H), 1.97 (d, $J=2.52$ Hz, 1H), 1.89 (d, $J=2.52$ Hz, 1H), 1.75-1.62 (m, 8H); $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ 199.92, 158.61, 127.89, 40.29, 39.14, 35.30, 33.36, 33.26, 32.97, 31.79, 28.22, 27.31; ESI-MS: Calculated for $\text{C}_{15}\text{H}_{20}\text{O}$ ($\text{M}+\text{H}$) $^+$ 217.3. Found: 217.4. S16 ((1r,3r,5r,7r)-spiro[adamantane-2,1'-cyclohexan]-4'-one) $^1\text{H-NMR}$ (360 MHz, CDCl_3) δ 2.30 (t, $J=6.84$ Hz, 4H), 2.09-2.05 (m, 4H), 1.95 (t, $J=6.84$ Hz, 4H), 1.90 (br s, 2H), 1.72 (br s, 4H), 1.65-1.61 (m, 4H); $^{13}\text{C-NMR}$ (90 MHz, CDCl_3) δ 213.04, 39.46, 36.95, 36.77, 34.36, 33.93, 33.03, 28.36; ESI-MS: Calculated for $\text{C}_{15}\text{H}_{22}\text{O}$ ($\text{M}+\text{H}$) $^+$ 219.3. Found: 219.4. S15 ((1r,3r,5r,7r)-spiro[adamantane-2,1'-cyclohexan]-4'-aminium chloride) $^1\text{H-NMR}$ (360 MHz, CD_3OD) δ 3.10-3.03 (m, 1H), 2.45-2.42 (m, 2H), 2.16-2.13 (m, 2H), 2.07-2.04 (m, 2H), 1.84 (br s, 1H), 1.84-1.82 (m, 4H), 1.73 (br s, 2H), 1.61-1.49 (6H), 1.26 (br s, 1H), 1.08-1.05 (m, 2H); $^{13}\text{C-NMR}$ (90 MHz, CD_3OD) δ 52.04, 40.73, 37.62, 33.97, 33.39, 30.70, 29.83, 26.69; ESI-MS: Calculated for $\text{C}_{15}\text{H}_{25}\text{N}$ ($\text{M}+\text{H}$) $^+$ 220.4. Found: 220.7.

Example 3

Structure Activity Relationship of Compounds

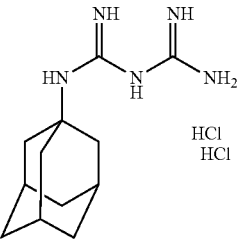
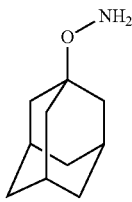
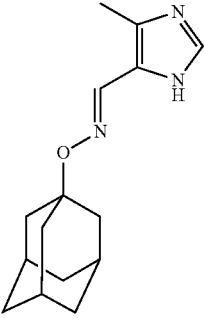
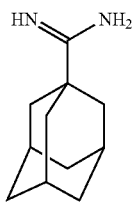
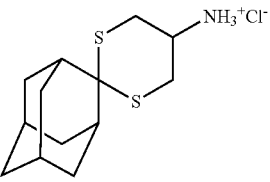
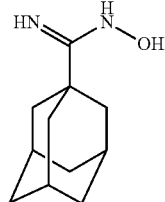
Table 1, below, shows the results of studies that were conducted to determine the activity, and in some cases, the IC_{50} , for exemplary inventive compounds. AM2 is the strain of influenza A virus on which the compounds were tested, and AM2(S31N) refers to AM2 virus that possesses the serine \rightarrow asparagine mutation at residue 31 in the M2 protein.

TABLE 1

Compounds	AM2		AM2 (S31N)	
	% inhibition at 100 uM	IC_{50} (μM)	% inhibition at 100 uM	IC_{50} (μM)
	38 (87%)		38 (20%)	
	39 (97%)		39 (0%)	
	40 (94%)		40 (0%)	

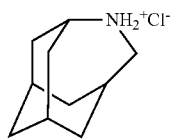
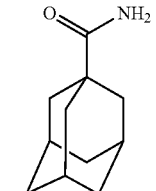
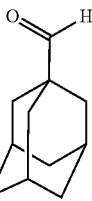
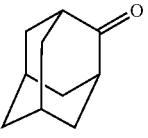
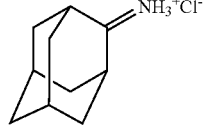
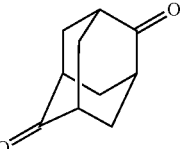
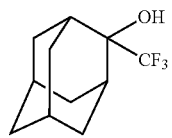
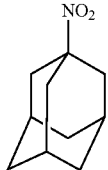
33

TABLE 1-continued

Compounds	AM2		AM2 (S31N)	
	% inhibition at 100 uM	IC50 (μM)	% inhibition at 100 uM	IC50 (μM)
 HCl HCl	41 (70%)		41 (0%)	
	42 (87%)		42 (15%)	
	43 (81%)		43 (10%)	
	44 (70%)		44 (31.5%)	
	45 (64%)		45 (0%)	
	46 (72.3%)		46 (0%)	

34

TABLE 1-continued

Compounds	AM2		AM2 (S31N)	
	% inhibition at 100 uM	IC50 (μM)	% inhibition at 100 uM	IC50 (μM)
5 	47 (83.8%)		47 (8%)	
10 	48 (74.9%)		48 (7.3%)	
15 	49 (65.1%)		49 (11%)	
20 	50 (69.6%)		50 (0%)	
25 	51 (92.3%)		51 (18.2%)	
30 	52 (59.1%)		52 (0%)	
35 	53 (82.9%)		53 (14%)	
40 	54 (87.2%)	54 (23.7)	54 (24%)	54 (647.2)
45				
50				
55				
60				
65				

35

Example 4

Structure Activity Relationship of Additional Compounds

Table 2, below, shows the results of studies that were conducted to determine the activity, and in some cases, the IC₅₀,

36

for additional exemplary inventive compounds. AM2 is the strain of influenza A virus on which the compounds were tested, and AM2(S31N) refers to AM2 virus that possesses the serine→asparagine mutation at residue 31 in the M2 protein. AM2(V27A) refers to AM2 virus that possesses the valine→alanine mutation at residue 27 in the M2 protein.

TABLE 2

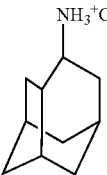
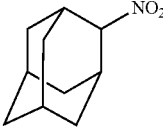
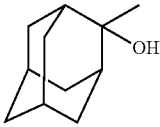
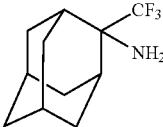
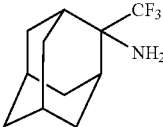
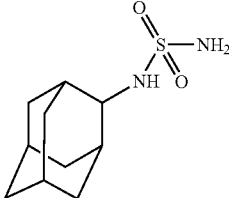
Compound	AM2		AM2 (S31N)		AM2 (V27A)	
	% inhibition at μM	IC ₅₀ (μM)	% inhibition at μM	IC ₅₀ (μM)	% inhibition at μM	IC ₅₀ (μM)
S1		94.2%		8.1%		236.1
S2						
S3		85.6%		12.4%		7.4%
S4						
S5		85.8%	13.5	10.6%		10.9%
S6						
S7		65.0%	64.6	13.8%		7.2%
S8						
S9		86.3%	10.1	13.7%		1.5%
S10						
S11		81.6%		3.8%		
S12						

TABLE 2-continued

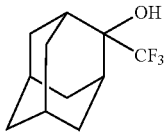
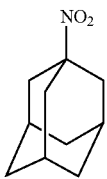
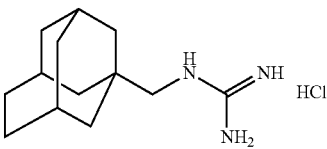
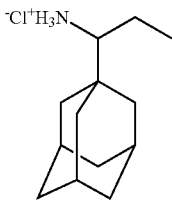
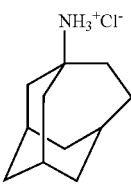
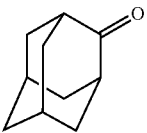
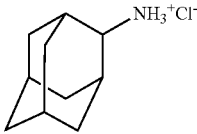
Compound	AM2		AM2 (S31N)		AM2 (V27A)	
	% inhibition at μM	IC ₅₀ (μM)	% inhibition at μM	IC ₅₀ (μM)	% inhibition at μM	IC ₅₀ (μM)
S8 	82.9%	13.8	14.0%		10.6%	
S9 	87.2%	23.7	24.0%	647.2	19.9%	
S10 						
S11 	91.5%		8.1%		25.5%	236.1
S12 	92%		32.8%		13.3%	
S13 	69.6%	28.8	0%		0%	
S14 	932.3%	14.3	18.2%	1495	0%	

Table 3, below, shows the results of studies that were conducted to determine the activity, and in some cases, the IC₅₀, for additional inventive compound S15. AM2 is the strain of influenza A virus on which the compounds were tested, and

S31N refers to AM2 virus that possesses the serine→asparagine mutation at residue 31 in the M2 protein. V27A refers to AM2 virus that possesses the valine→alanine mutation at residue 27 in the M2 protein.

TABLE 3

	AM2 wt (mean ± SE) Oocytes		S31N (mean ± SE) Oocytes		V27A (mean ± SE) Oocytes	
	% of inhibition by 100 μM 2 min	IC ₅₀ (μM)	% of inhibition by 100 μM for 2 min	IC ₅₀ (μM)	% of inhibition by 100 μM for 2 min	IC ₅₀ (μM)
Amantadine	90.8 ± 2.5	16.0	34.7 ± 1.6	199.9		
Rimantadine	91.2 ± 0.9	10.8	13.3 ± 1.8	N.M.		
S15	89.1 ± 1.3		2.1 ± 1.1		94.5 ± 0.4	0.31

Chemical Formula: C₁₅H₂₆ClN

Molecular Weight: 255.83

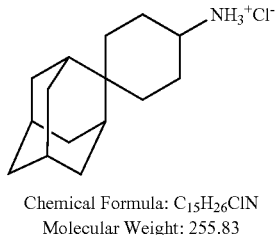
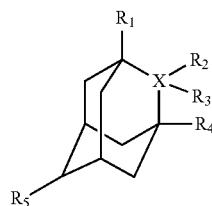


FIG. 1 depicts dose response curves for compound S15 on the inhibition of wild-type influenza virus, as well as on the V27A, L26F, and S31N mutants.

What is claimed:

1. A compound having the formula (I):



wherein

X is carbon, $\text{—NH(H}^+\text{Cl}^-)$, alkylene, or alkyleneamino; R₁ is hydrogen, deuterium, halo, hydroxyl, nitro, guanidiny, $\text{—(R}_6\text{)—guanidine}$, formamidiny, carbonyl, oxime, amino, aminocarbonyl, aminooxy, aralkoxy, or aralkylaminooxy;

R₂ and R₃ are each independently hydrogen, deuterium, hydroxyl, carbonyl, amino, nitro, alkyl, trifluoromethyl, aryl, aminocarbonyl, or —C(=Y)—Z ,

or

R₂ and R₃ taken together along with the atom to which they are both attached form a six-membered carbocyclic ring or a dithanyl ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl;

Y is O, S, or NH;

Z is amino, —NH—NH_2 , methoxy, or methylthio;

R₄ is hydrogen, deuterium, or amino;

R₅ is hydrogen or carbonyl; and,

R₆ is $\text{—CH(CH}_3\text{)—}$ or —NH—C(=NH)— ;

or a stereoisomer, partial stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof,

with the proviso that if R₁ is amino and X is methylene or ethylene, R₂, R₃, R₄, and R₅ cannot all be hydrogen.

2. The compound according to claim 1 wherein X is carbon, and R₂, R₃, R₄, and R₅ are each hydrogen.

3. The compound according to claim 2 wherein R₁ is guanidiny, $\text{—(R}_6\text{)—guanidine}$, formamidiny, carbonyl, oxime, nitro, aminocarbonyl, aminooxy, aralkoxy, or aralkylaminooxy.

4. The compound according to claim 3 wherein R₆ is $\text{—CH(CH}_3\text{)—}$ or —NH—C(=NH)— .

5. The compound according to claim 3 wherein R₁ is (5-methyl-3H-imidazol-4-ylmethylene)-aminoxy or hydroxyamino(imino)methyl.

6. The compound according to claim 1 wherein R₁ and R₅ are both hydrogen.

7. The compound according to claim 6 wherein R₂ is hydrogen and R₃ is hydrogen, hydroxyl, carbonyl, amino, nitro, or —C(=Y)—Z .

8. The compound according to claim 7 wherein X is $\text{—NH(H}^+\text{Cl}^-)$ and R₃ is hydrogen, hydroxyl, amino, or —C(=Y)—Z .

9. The compound according to claim 6 wherein R₂ and R₃ taken together along with the atom to which they are both attached form a six-membered carbocyclic ring or a dithanyl ring optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl.

10. The compound according to claim 9 wherein R₂ and R₃ taken together form [1,3]Dithian-5-ylamine.

11. The compound according to claim 9 wherein R₂ and R₃ taken together form cyclohexane optionally substituted with up to three substituents independently selected from alkyl, aryl, aralkyl, hydroxyl, nitro, amino, and carbonyl.

12. The compound according to claim 6 wherein R₄ is hydrogen, and R₂ and R₃ are independently selected from hydroxyl, trifluoromethyl, alkyl, amino, nitro, or aryl.

13. The compound according to claim 1 wherein said compound is

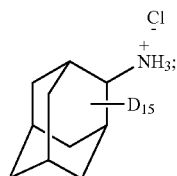
N-Adamantan-1-yl-guanidine;

N-(1-Adamantan-1-yl-ethyl)-guanidine;

O-Adamantan-1-yl-hydroxylamine;

41

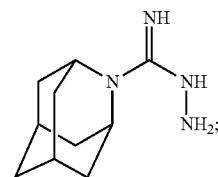
5-Methyl-3H-imidazole-4-carbaldehyde O-adamantan-1-yl-oxime;
 Adamantane-1-carboxamidine;
 Adamantane amidine hydrochloride;
 2,2-spiro adamantyl-1,3-dithian-5-aminium chloride;
 N-Hydroxy-adamantane-1-carboxamidine;
 4-Aza-tricyclo[4.3.1.13,8]undecane;
 4-Azoniatricyclo[4.3.1.13,8]undecane chloride;



Adamantane-1-carbaldehyde;
 Adamantan-2-amine; Adamantane-2,6-dione;
 2-Trifluoromethyl-adamantan-2-ol;
 2-(4-amino-cyclohexyl)-adamantane;
 1-Nitro-adamantane;
 2-Nitro-adamantane;
 2-Methyl-adamantan-2-ol;
 2-Methyl-adamantan-2-ylamine;
 2-Methyl-2-nitro-adamantane;
 2-Trifluoromethyl-adamantan-2-ylamine;
 2-(1H-Pyrazol-3-yl)-adamantan-2-ol;
 2-Aza-tricyclo[3.3.1.13,7]decan-2-ol; Adamantane-1-carboximidic acid methyl ester;

42

2-Aza-tricyclo[3.3.1.13,7]decane;
 2-Aza-tricyclo[3.3.1.13,7]decan-2-ol;
 2-Aza-tricyclo[3.3.1.13,7]dec-2-ylamine;
 2-Aza-tricyclo[3.3.1.13,7]decane-2-carboxylic acid
 amide;
 2-Aza-tricyclo[3.3.1.13,7]decane-2-carbothioic acid
 amide;
 2-Aza-tricyclo[3.3.1.13,7]decane-2-carboxamidine;
 2-Aza-tricyclo[3.3.1.13,7]decane-2-carboximidic acid
 methyl ester;
 2-Aza-tricyclo[3.3.1.13,7]decane-2-carboximidothioic
 acid methyl ester;



2-Aza-tricyclo[3.3.1.13,7]decan-1-ol;
 1-Chloro-2-aza-tricyclo[3.3.1.13,7]decane;
 or a stereoisomer, partial stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, and N-oxide thereof.

14. A composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, diluent, or excipient.

* * * * *